Exhibit 28

**WORLD HEALTH ORGANIZATION**
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 93

Carbon Black, Titanium Dioxide, and Talc
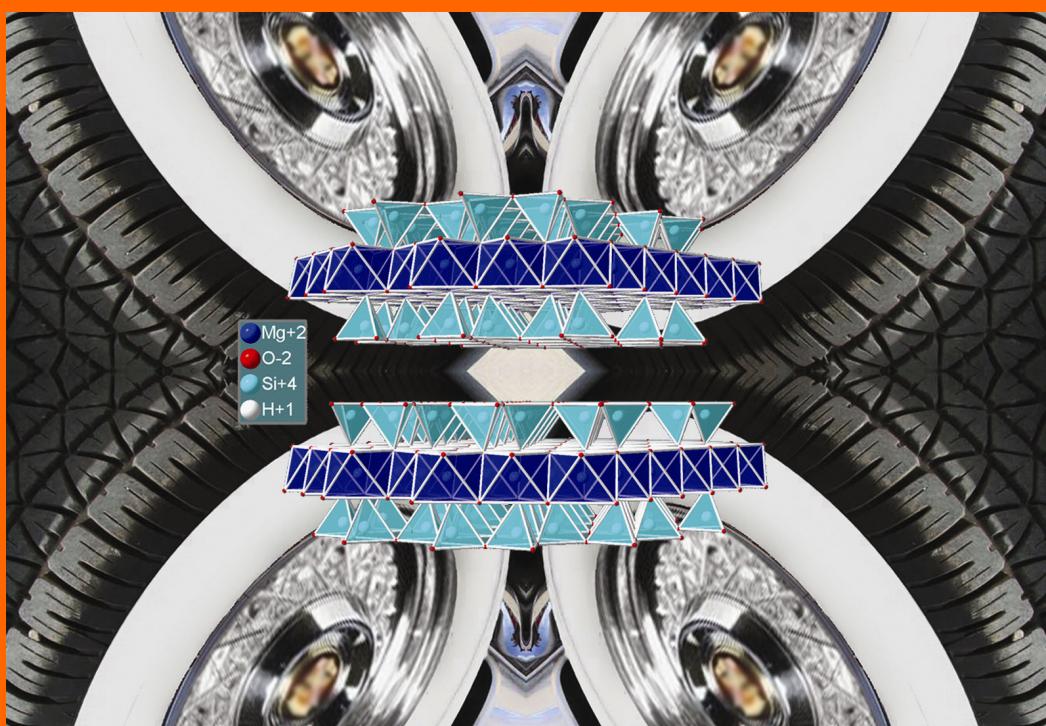
LYON, FRANCE
2010

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 93

Carbon Black, Titanium Dioxide, and Talc

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

7–14 February 2006

2010

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

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Cover photograph: The white-wall automobile tyre represents carbon black and titanium dioxide; the chemical structure illustrates the platy structure of talc (see Section 1 for details).

CONTENTS

CONTENTS   vii

viii   IARC MONOGRAPHS VOLUME 93

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer under some circumstances. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

VOLUME 93
CARBON BLACK, TITANIUM DIOXIDE, AND TALC

Lyon, 7–14 February 2006

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[2] Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 3 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$10 000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[3] Received past research support from the International Carbon Black Association, comprised of companies that manufacture carbon black.

[4] Department receives research support from CEFIC (European Chemical Industry Council); this does not exceed 5% of the department's budget and does not support the expert's own research or position.

[5] Received travel support for a January 2006 meeting sponsored in part by the International Carbon Black Association.

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[8] Participation funded by the US National Cancer Institute under a contract to Technical Resources International Inc. and a subcontract to the International Life Sciences Institute.

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[10] Employer is conducting research sponsored by the International Carbon Black Association. Past service as a scientific advisor to the International Carbon Black Association. Received travel support for a January 2006 meeting sponsored in part by the International Carbon Black Association.

[11] Consultant to the Industrial Minerals Associations of Europe and of North America. Currently submitting publications supported by prior grants from the International Carbon Black Association. Received travel support for a January 2006 meeting sponsored in part by the International Carbon Black Association.

[12] Employed by the DuPont Company, a manufacturer of titanium dioxide and user of carbon black and talc in some products. Received travel support for a January 2006 meeting sponsored in part by the International Carbon Black Association.

6   IARC MONOGRAPHS VOLUME 93

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PREAMBLE

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when

IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

PREAMBLE   11

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally,

doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph,* or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers

from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on

analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary

analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

    1. Exposure data

    2. Studies of cancer in humans

    3. Studies of cancer in experimental animals

    4. Mechanistic and other relevant data

    5. Summary

    6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a)   General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b)   Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c)   Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d)   Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings

from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e)   *Regulations and guidelines*

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a)   *Types of study considered*

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b)   Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis,

by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c)   Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo

analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group

considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified

constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a)   Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b)   Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c)   Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and

are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a)   Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) *Data on mechanisms of carcinogenesis*

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) *Changes in physiology*

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) *Functional changes at the cellular level*

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) *Changes at the molecular level*

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio

et al., 1992; McGregor *et al*., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al*., 1986; McGregor *et al*., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al*., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al*., 1986; McGregor *et al*., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations

that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c)   Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d)   Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to

differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e)   Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(a)   Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b)   Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c)   Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d)   Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a)   Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b)   Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single

species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c)   *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of

biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d)   Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1:   The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of

carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3:   The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4:   The agent is *probably not carcinogenic to humans*.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e)   Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This ninety-third volume of *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of three chemically inert, poorly soluble particles: carbon black, titanium dioxide, and talc. In 2003 an Advisory Group on priorities for future evaluation recommended that carbon black and titanium dioxide be considered with high priority (IARC 2003), and in 2004 an Advisory Group to plan a series of *IARC Monographs* on air pollution recommended that these particles be reviewed before complex mixtures such as diesel engine exhaust. Talc is included in this volume because as an inhaled particle it has many features in common with carbon black and titanium dioxide, and as a consumer product it has been the subject of an abundance of epidemiological studies. Each of the three agents in this volume has been reviewed before. Carbon black was evaluated in Volume 65, titanium dioxide in Volume 47, and talc not containing asbestiform fibres in Supplement 7. New epidemiological and experimental studies are reviewed in this volume.

This volume does not review carbon-based particles of more complex or variable composition, such as activated charcoal, toner, charbone, and soot. This volume also does not review ultrafine and engineered nano-forms of these particles, because there are few pertinent studies. The physical properties and mechanistic studies of ultrafine and nanoparticles that are reviewed in this volume suggest that these smaller particles, due to their greater surface area per unit of mass, may be more effective in inducing toxic effects.

The review of talc in Supplement 7 led to evaluations for two agents: talc containing asbestiform fibres and talc not containing asbestiform fibres. The term 'asbestiform fibre' has been mistaken as a synonym for 'asbestos fibre' when it should be understood to mean any mineral, including talc, when it grows in an asbestiform habit. To avoid confusion over the term 'asbestiform fibre', the present Working Group decided that it is scientifically more precise to call the agent 'talc not containing asbestos or asbestiform fibres', and this evaluation supersedes the earlier review of talc not containing asbestiform fibres. The present Working Group also decided to expand the name of the Group-1 agent from 'talc containing asbestiform fibres' to 'talc containing asbestos or other asbestiform fibres'. The present Working Group reviewed the earlier *Monograph* on talc containing asbestiform fibres and determined that the expanded name is consistent with what had been evaluated in Supplement 7. No update was undertaken for this Group-1 agent.

40   IARC MONOGRAPHS VOLUME 93

This volume is the first to use the 2006 version of the Preamble, which was amended during 2005 through an open process that solicited comments from the scientific community and peer review by an Advisory Group (IARC, 2006). Another innovation that is being tried for the first time is the consideration of public nominations for expert scientists, several of whom are serving on this Working Group.

A summary of the findings of this volume appears in *The Lancet Oncology* (Baan *et al.*, 2006).

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THE MONOGRAPHS

CARBON BLACK

Carbon black has been considered by previous Working Groups in April 1984, March 1987 and October 1995 (IARC, 1984, 1987, 1996). Since that time, new data have become available, and these have been included in the present monograph and have been taken into consideration in the evaluation.

1. Exposure Data

1.1   Chemical and physical data

1.1.1   *Nomenclature*

The Chemical Abstract Service Registry Number for all carbon blacks is 1333–86–4.

Acetylene black

Chem. Abstr. Name: Carbon black, acetylene
IUPAC Systematic Name: Carbon black, acetylene
Synonyms: CI: 77266; CI Pigment Black 7; explosion acetylene black; explosion black
Trade names: P68, P1250, Shawinigan Acetylene Black and Ucet

Channel black

Chem. Abstr. Name: Carbon black, channel
IUPAC Systematic Name: Carbon black, channel
Synonyms: CI: 77266; CI Pigment Black 7; impingement black
Trade names: Aroflow, Arrow, Atlantic, Black Pearls, Carbolac, Carbomet, CK3, Collocarb, Conductex (Continental), Croflex, Crolac, Degussa, Dixie, Dixiecell, Dixiedensed, Elf, Excelsior, Farbruss, Fecto, Huber, Kosmink, Kosmobil, Kosmolak, Kosmos, Kosmovar, Micronex, Mogul, Monarch, Neo-Spectra, Peerless, Printex, Raven, Regent, Royal Spectra, Special Black IV & V, Spheron, Superba, Super-Carbovar, Super-Spectra, Texas, Triangle, United, Witco and Wyex

Furnace black

Chem. Abstr. Name: Carbon black, furnace
IUPAC Systematic Name: Carbon black, furnace
Synonyms: CI: 77266; CI Pigment Black 7; gas-furnace black; oil-furnace black
Trade names: Aro, Arogen, Aromex, Arovel, Arotone, Atlantic, Black Pearls, Carbodis, Collocarb, Conductex (Continex), Corax, Croflex, Dixie, Durex, Elftex, Essex, Furnal, Furnex, Gastex, Huber, Humenegro, Kosmos, Metanex, Modulex, Mogul, Molacco, Monarch, Neotex, Opal, Peerless, Pelletex, Philblack, Printex, Rebonex, Regal, Special Schwarz, Statex, Sterling, Texas, Ukarb, United and Vulcan

Lampblack

Chem. Abstr. Name: Carbon black, lamp
IUPAC Systematic Name: Carbon black, lamp
Synonyms: CI: 77266; CI Pigment Black 6
Trade names: Carbon Black BV and V, Durex, Eagle Germantown, Flamruss, Magecol, Tinolite and Torch Brand

Thermal black

Chem. Abstr. Name: Carbon black, thermal
IUPAC Systematic Name: Carbon black, thermal
Synonyms: CI: 77266; CI Pigment Black 7; therma-atomic black
Trade names: Atlantic, Cancarb, Croflex, Dixitherm, Huber, Kosmotherm, Miike 20, P-33, Sevacarb, Shell Carbon, Statex, Sterling, Thermatomic, Thermax, Thermblack and Velvetex

1.1.2   *General description*

Carbon black is a generic term for an important family of products that is used principally for the reinforcement of rubber, as a black pigment and because of its electrically conductive properties. It is an extremely fluffy fine powder with a large surface area and is composed essentially of elemental carbon. Carbon black is one of the most stable chemical products. In general, it is the most widely used nanomaterial and its aggregate dimension ranges from tens to a few hundred nanometers (nm); it imparts special properties to composites of which it is a part.

Plants for the manufacture of carbon black are strategically located worldwide to supply the rubber tyre industry, which consumes 70% of the carbon black produced. About 20% is used for other rubber products and 10% is used for a variety of non-rubber applications. World capacity in 2005 was estimated at more than 10 million tonnes (Auchter, 2005). Over 40 grades (listed in ASTM International, 2005a) are used by the rubber industry alone. Many additional grades are marketed for non-rubber applications (Voll & Kleinschmit, 2002; Wang *et al.*, 2003; ASTM International, 2005a).

Carbon black is a form of elemental carbon that is manufactured by the controlled vapour-phase pyrolysis and partial combustion of hydrocarbons. Several processes have been used to produce carbon black, including the oil-furnace, impingement (channel), lampblack, thermal (decomposition of natural gas) and acetylene (decomposition) processes. Carbon blacks are commonly referred to by the process or the source material from which they are made, e.g. furnace black, lampblack, thermal black, acetylene black and channel black. The different grades from the various processes have certain unique characteristics, but it is now possible to produce reasonable approximations of most of these grades using the oil-furnace process, by which more than 95% of the total output of carbon black is produced (Voll & Kleinschmit, 2002; Wang *et al.*, 2003).

In contrast to carbon black, soot is a material of varying and often unknown composition that is an unwanted by-product of the incomplete combustion of all types of material that contain carbon, such as waste oil, coal, paper, rubber, plastic, household waste and also some fuel oils. Soots have a small surface area of available carbon due to their large particle size and low carbon content. They typically contain large quantities of solvent-extractable materials and their ash content can be 50% or more (European Committee for Biological Effects of Carbon Black, 1982; Voll & Kleinschmit, 2002; Wang *et al.*, 2003).

Two other commercial carbonaceous products are activated carbon (including activated charcoal) and bone black. Activated carbon is a collective name for a group of porous carbons, which are manufactured either by the treatment of carbon with gases or by the carbonization of carbonaceous materials with simultaneous activation by chemical treatment. Activated carbon possesses a porous structure, usually has small amounts of chemically bonded oxygen and hydrogen and can contain up to 20% of mineral matter, which usually consists of ash or residue as a result of ignition. The nature of this mineral material depends on the raw materials used, and can consist of silica and compounds of alkali and alkaline-earth metals, for example. X-Ray investigations show that the carbon is mainly in the form of very small crystallites with a graphite-like structure (Vohler *et al.*, 1986).

Bone black is a pigment that is derived as a by-product of the manufacture of bone char, which is made by carbonizing bones and is used principally in sugar refining. Bone black is used primarily as a colourant in artists' paint and for tinting vinyl fabrics for upholstery and automotive interiors. The carbon content of bone black is usually approximately 10% (Lewis, 1988, 1993).

Soot, activated carbon and bone black, as well as other forms of carbonaceous products, are not considered in this monograph.

1.1.3   *Chemical and physical properties of the technical products*

(a)   Particle size

Different types of carbon black have a wide range of primary particle sizes, large surface areas per unit mass, low contents of ash and solvent-extractable materials and

varying degrees of particle aggregation. A carbon black with a high degree of aggregation is said to have a high 'structure'. Structure is determined by the size and shape of the aggregated primary particles, the number of primary particles per aggregate and their average mass.

Carbon black is initially formed as roughly spherical primary particles, which, in most cases, rapidly form aggregates. An aggregate is a chain of primary carbon particles that are permanently fused together in a random branching structure. The aggregate may consist of a few or hundreds of spherical particles (or, as in the case of thermal black, primarily single spheres rather than chains). The chains are open structures and are used to absorb fluids and reinforce materials such as rubber. The aggregates can bind together by van der Waals forces in more loosely associated agglomerates, or they may be compressed into pellets (up to 0.5 cm) that are held together by means of binders (molasses and/or lignosulfonates) (Dannenberg *et al.*, 1992; Gardiner *et al.*, 1992a).

Two dimensions are necessary to define a carbon black aggregate. (1) *Mean diameter of the component spheres in the chain*: this is a measure of the 'thickness' of the chain, is called the primary particle size and is generally inversely proportional to the surface area of the carbon black. (2) *Extent of the branched chain aggregate*: this is called the aggregate size and is the dimension of the rigid framework that is the aggregate.

In addition to these two dimensions, there is a property or 'structure' which is the volume of space that is 'reinforced' by the aggregate—essentially, the amount of fluid it can absorb internally. A standard method of measuring this property is by the dibutyl phthalate absorption of a carbon black (in units of millilitres per 100 g).

The properties and grades of carbon black that largely determine its use are related to structure, surface area and condition. Over the years, a system for the designation of types was developed in the production and consumer industries which used the initial letters of words that describe a particular carbon black. For example, HAF stood for high-abrasion furnace black, and SRF stood for semi-reinforcing furnace black. These generic designations have largely been replaced by the technical classification system developed by the American Society for Testing and Materials (ASTM). This system, originally adopted in 1966, is primarily for rubber-grade carbon blacks and consists of a letter followed by a three-digit number. Thus, the letter N stands for normal cure of a rubber compound and the first digit following the letter designates the group number, which is determined by the average primary particle size as measured by electron microscopy. The particle range of rubber-grade carbon black is arbitrarily divided into 10 groups, as shown in Table 1.1. The third and fourth characters of this system are numbers that are assigned arbitrarily. For example, HAF black has ASTM number N330 (ASTM International, 2005a).

More than 40 grades of carbon black are currently in use in the rubber industry and all contribute to the physical properties of the finished rubber product, such as tensile strength and resistance to abrasion. Almost as many specialty grades (some of which are re-brands of the standard rubber-grade carbon blacks) are used in the paint, plastics, ink

and other such industries. In these applications, particle size and surface characteristics contribute to tinting strength and blackness.

Table 1.2 presents a summary of surface area and primary particle size, aggregate diameter and agglomerate size for different types of carbon black.

Table 1.1. Particle range of rubber-grade carbon blacks

Group number	Typical average primary particle size (nm)	Average surface area (m^2/g)
0	0–10	>150
1	11–19	121–150
2	20–25	100–120
3	26–30	70–99
4	31–39	50–69
5	40–48	40–49
6	49–60	33–39
7	61–100	21–32
8	101–200	11–20
9	201–500	0–10

From Auchter (2005)

Table 1.2. Summary information on particle size

Carbon black	Surface area (m^2/g)	Approximate diameter of primary particle size (nm)	Diameter of aggregate (nm)	Size of agglomerate
Oil-furnace	12–240	10–400	50–400	Large (<2 mm)
Thermal	6–15	120–500	400–600	Large (<2 mm)
Impingement (channel)		10–30	50–200	Large (<2 mm)
Lampblack	15–25	60–200	300–600	Large (<2 mm)
Acetylene black	15–70	30–50	350–400	Pelletizes poorly

Compiled by the Working Group from Kuhlbusch *et al.* (2004); Kirk-Othmer (2005)

(b)   Production processes, raw materials and uses

Table 1.3 lists some of the major types of carbon black that are available, together with data on production process, raw materials and major use properties in the compounding of elastomers. Within each of the groups listed, several commercial modifications have been made; for example, one producer alone lists five different grades of intermediate superabrasion furnace carbon black, including low structure, low modulus, high structure and others (Auchter, 2005). Table 1.4 provides the ASTM

designations for furnace blacks used in rubber, three typical measures of surface area (iodine adsorption, nitrogen absorption and statistical thickness) and one measure of the degree of aggregation (dibutyl-phthalate absorption). Table 1.5 provides similar information for furnace blacks used in inks, paints and plastics.

Table 1.3. Grades, production processes, selected properties and uses of carbon black

Type	Designation		Production process and/or feedstock	Average primary particle diameter (nm)	Iodine absorption number[a] (g/kg)	Primary rubber processing properties and use
	Acronym	ASTM				
Superabrasion furnace black	SAF	N110	Oil furnace	17	145	High reinforcement; used in special and off-road tyre products for which high abrasion resistance is required.
Intermediate superabrasion furnace black	ISAF	N220	Oil furnace	21	121	High reinforcement and tear strength, good processing; used in passenger, off-road and special tyres for which good abrasion resistance is required.
High-abrasion furnace black	HAF	N330	Oil furnace	31	82	Medium-high reinforcement, low modulus, high elongation, good flex, tear and fatigue resistance; used in tyre tread, carcass and sidewall compounds, motor mounts, weather-stripping and bicycle tyres
Fast-extruding furnace black	FF	N550	Oil furnace	53	43	Medium-high reinforcement, high modulus and hardness, low die swell and smooth extrusion; used in tyre inner liners, carcass and sidewall compounds and hose and other extruded goods
General-purpose furnace black	GPF	N660	Oil furnace	63	36	Medium reinforcement and modulus, good flex and fatigue resistance, low heat build-up; used in tyre carcass, inner liners and sidewalls, sealing rings, cable jackets, hose and extruded goods
Semi-reinforcing furnace black	SRF	N762	Oil furnace	110	27	Medium reinforcement, high elongation and resilience, low compression set; used in mechanical goods, footwear, inner tubes and floor mats
Medium thermal black	MT	N990	Natural gas	320	9	Low reinforcement, low modulus, hardness, hysteresis and tensile strength, high elongation and loading capacity; used in wire insulation and jackets, mechanical goods, footwear, belts, hose, gaskets, O-rings and tyre inner liners

From Auchter (2005) [from Dannenberg (1978); Lyon & Burgess (1985)]
[a] Used as a measure of surface area, which is an indication of reinforcement ability

Table 1.4. Typical properties of rubber-grade carbon blacks

ASTM Classification	Iodine adsorption (g/kg)	NSA (m^2/g)	STSA (m^2/g)	DBPA (mL/100 g)
N110	145	127	115	113
N115	160	137	124	113
N120	122	126	113	114
N121	121	122	114	132
N125	117	122	121	104
N134	142	143	137	127
N135	151	141	–	135
S212	–	120	107	85
N219	118	–	–	78
N220	121	114	106	114
N231	121	111	107	92
N234	120	119	112	125
N293	145	122	111	100
N299	108	104	97	124
S315	–	89	86	79
N326	82	78	76	72
N330	82	78	75	102
N335	92	85	85	110
N339	90	91	88	120
N343	92	96	92	130
N347	90	85	83	124
N351	68	71	70	120
N356	92	91	87	154
N358	84	80	78	150
N375	90	93	91	114
N539	43	39	38	111
N550	43	40	39	121
N582	100	80	–	180
N630	36	32	32	78
N642	36	39	–	64
N650	36	36	35	122
N660	36	35	34	90
N683	35	36	34	133
N754	24	25	24	58
N762	27	29	28	65
N765	31	34	32	115
N772	30	32	30	65
N774	29	30	29	72
N787	30	32	32	80
N907	–	9	9	34
N908	–	9	9	34
N990	–	8	8	43
N991	–	8	8	35

From ASTM International (2005a)
NSA, nitrogen surface area; STSA, statistical thickness surface area; DBPA, dibutyl phthalate absorption

Table 1.5. Typical properties of furnace blacks used in inks, paints, paper and plastics

Furnace black	Surface area[a] (m^2/g)	Primary particle size (nm)	DBPA (mL/100 g)		Bulk density (g/L)		Volatile content (%)
			Fluffy	Pellets	Fluffy	Pellets	
Normal furnace grades							
High colour	250–300	14–15	70–75	60–65	50–300	400–550	1.2–2.0
Medium colour	150–220	16–24	47–122	46–117	130–300	390–550	1.0–1.5
Regular colour	45–140	20–37	42–125	42–124	176–420	350–600	0.9–1.5
Low colour	24–45	41–75	71	64–120	256	352–512	0.6–0.9
Surface oxidized grades							
High colour	400–600	10–20	121	105	–	–	8.0–9.5
Medium colour (long flow)	100–138	23–24	49–60	55	240–360	530	3.5–5.0
Medium colour (medium flow)	96–110	25	49–72	70	225–360	480	2.5–3.5
Low colour	30–40	50–56	48–93	–	260–500	–	3.5

From Dannenberg *et al*. (1992)

DBPA, dibutyl-phthalate absorption

[a] Calculated by the Brunauer, Emmett and Teller (BET) procedures

Furnace black can be produced with a wide range of properties. Thermal black typically has the largest particle size and smallest surface area of the carbon blacks, with spherical particles, a low degree of aggregation and low oxygen content. Lampblack is characterized by a high degree of aggregation of mid-size particles and small surface area. Acetylene black is typically very pure (carbon content, ~99.7%) with an extremely high degree of aggregation and is the most crystalline or graphitic of the carbon blacks. Characteristics of channel black include small particle size and a high level of surface oxidation (Dannenberg *et al.*, 1992; Wang *et al.*, 2003).

1.1.4   *Extractable impurities in carbon black*

Because of their source materials, the methods of their production and their large surface areas and surface characteristics, commercial carbon blacks typically contain varying quantities of adsorbed by-products from the production process, particularly aromatic compounds. Several methods have been developed and used to extract and characterize these adsorbed chemicals (see Section 1.1.5(*b*)). The classes of chemical most commonly identified in these extracts are polycyclic aromatic hydrocarbons

(PAHs), nitro derivatives of PAHs (nitro-PAHs) and PAHs that contain sulfur. Examples of these three classes of chemical identified in carbon black extracts are given in Table 1.6.

Table 1.6. Some compounds identified in carbon black extracts

Polycyclic aromatic hydrocarbons (PAHs)	Fluorene
(see also IARC, 1984, 2010)	Indeno[1,2,3-*cd*]pyrene
Acenaphthene	Naphthalene
Acenaphthylene	Perylene
Anthanthrene	Phenanthrene
Anthracene	Pyrene
Benz[*a*]acenaphthylene	*Nitro derivatives of PAHs* (nitro PAHs) (see also
Benz[*a*]anthracene	IARC, 1987)
Benzo[*b*]fluoranthene	1,3-Dinitropyrene
Benzo[*ghi*]fluoranthene	1,6-Dinitropyrene
Benzo[*j*]fluoranthene	1,8-Dinitropyrene
Benzo[*k*]fluoranthene	9-Nitroanthracene
Benzo[*a*]pyrene	3-Nitro-9-fluorenone
Benzo[*e*]pyrene	1-Nitronaphthalene
Benzo[*ghi*]perylene	1-Nitropyrene
Chrysene	1,3,6-Trinitropyrene
Coronene	*PAHs that contain sulfur*
4*H*-Cyclopenta[*def*]phenanthrene	Benzo[*def*]dibenzothiophene
Cyclopenta[*cd*]pyrene	Dibenzothiophene
Dibenz[*ah*]anthracene	Phenanthro[4,5-*bcd*]thiophene
Fluoranthene	Triphenyleno[4,5-*bcd*]thiophene

Modified from IARC (1996)

The specific chemicals detected in carbon black extracts and their relative quantities vary widely from sample to sample. Extraction method, type and grade of carbon black and post-extraction treatments all appear to be factors that affect the type and quantity of impurities obtained, and substantial batch-to-batch variation is typical.

Benzo[*ghi*]perylene, coronene, cyclopenta[*cd*]pyrene, fluoranthene and pyrene are among the PAHs frequently found at the highest levels in carbon black extracts. For example, in a study of five types of furnace black used in tyre manufacture, extraction with hot benzene after 250 hours yielded means of 252–1417 mg extract/kg carbon black. The quantities of various PAHs found in the extracts were as follows (mg/kg): anthanthrene, < 0.5–108; benzacridine derivative, < 0.5; benzo[*def*]dibenzothiophene and benzo[*e*]acenaphthylene, < 0.5; benzofluoranthenes (total), < 0.5–17; benzo[*ghi*]fluoranthene, 20–161; benzo[*ghi*]perylene, 23–336; benzopyrenes (total), 2–40; cyclopenta[*cd*]pyrene, < 0.5–264; coronene and isomer, 13–366; dimethylcyclopentapyrene and/or dimethylbenzofluoranthene, 2–57; fluoranthene, 10–100; indeno[1,2,3-*cd*]pyrene, 1–59; phenanthrene and/or anthracene, < 0.5–5; and pyrene, 46–432 (Locati *et al.*, 1979). The results of two similar studies that used benzene

to extract adsorbates from several oil-furnace blacks and one thermal black are shown in Table 1.7 (Taylor *et al.*, 1980; Zoccolillo *et al.*, 1984).

Table 1.7. Concentrations of total extractable adsorbate and benzo[*a*]pyrene in the benzene extracts of 10 carbon blacks

ASTM designation[a]	Surface area (m^2/g)	Total extract (mg/kg) (no. of samples)	Concentration of benzo[*a*]pyrene (mg/kg) (no. of samples)
N220	118	250 (2)	0.29 (4)
N234	128	630 (2)	1.08 (5)
N326	80	225 (1)	0.18 (1)
N339	90	510 (4)	1.46 (2)
N347	90	343 (1)	0.50 (1)
N351	70	780 (3)	5.47 (5)
N375	101	1020 (5)	3.81 (2)
N550	42	610 (1)	0.14 (1)
N660	36	653 (6)	4.80 (6)
N990[b]	10	8020 (1)	35.00 (1)

From Taylor *et al.* (1980); Zoccolillo *et al.* (1984)
[a] For American Society for Testing and Materials designations of types, see Tables 1.3 and 1.4.
[b] N990 is a thermal black.

PAH fractions from six different batches of the same furnace black (ASTM N660) were analysed and ranged from 200 to 736 mg/kg; benzo[*a*]pyrene concentrations ranged from 1.2 to 9.7 mg/kg in benzene extracts (Zoccolillo *et al.*, 1984).

Seven types of carbon black used in tyre production in Poland (domestic: JAS-220, JAS-330, JAS-530; imported: HAF-N-326, HAF-N-330, SRF-N-762 and Dure × −0) were analysed. Toluene-soluble extractable compounds, including PAHs, were determined by a gravimetric method and benzo[*a*]pyrene by high-performance liquid chromatography (HPLC) with a spectrometric detector. Toluene-soluble compounds amounted to 0.12–0.25% (by weight). Benzo[*a*]pyrene, at a range of 1.44–3.07 ppm [mg/kg], was detected in five of the seven carbon blacks examined (Rogaczewska *et al.*, 1989).

Agurell and Löfroth (1993) studied the variation in impurities of a furnace carbon black (ASTM N330) manufactured in Sweden over a 3-year period. The PAHs that were determined in benzene extracts and their ranges of concentration (mg/kg carbon black) were: phenanthrene, 0.9–15; fluoranthene, 4.5–72; pyrene, 26–240; benzo[*ghi*]fluoranthene, 7.2–72; cyclopenta[*cd*]pyrene, 6.6–188; chrysene, 0.1–1.3; benzo[*b*]fluoranthene, benzo[*j*]fluoranthene and benzo[*k*]fluoranthene, 0.4–18; benzo[*e*]pyrene, 0.9–19; benzo[*a*]pyrene, 0.9–28; perylene, 0.1–3.5; indeno[1,2,3-*cd*]pyrene, 2–43; benzo[*ghi*]perylene, 14–169; and coronene, 14–169.

Somewhat higher total levels of PAHs were found in extracts of thermal blacks. A 24-hour benzene extract of an ASTM N990-type thermal black yielded approximately 4000 mg extract/kg carbon black. Individual PAHs (mg/kg) included: benzo[*ghi*]perylene (1217), coronene (800), pyrene (603), anthanthrene (299), fluoranthene (197), benzo[*a*]pyrene (186) and benzo[*e*]pyrene (145) (De Wiest, 1980). The total level of PAHs in the benzene extract of another sample of ASTM N990 thermal black was 2140 mg/kg, which included 35 mg/kg benzo[*a*]pyrene (Zoccolillo *et al.*, 1984).

Typical and specified PAH contents were compared for three samples of thermal black and two of furnace black. Levels of benzo[*a*]pyrene ranged from 0.03 to 0.2 ppm in the thermal black samples and up to 0.001 ppm in the furnace blacks; levels of total PAHs ranged from 1.5 to 9.2 ppm in the thermal black samples and from 0.01 to 0.26 ppm in the furnace black samples (Cabot Corporation, 2005a).

Nitro PAHs were identified in extracts of some samples of channel black and furnace black that had been subjected to oxidative treatment with nitric acid. Discovery of these by-products in a photocopy toner in the late 1970s led to modifications of the oxidative process; these changes have reportedly eliminated the presence of nitro PAHs in commercial furnace blacks that have been produced since 1980 (Fitch *et al.*, 1978; Fitch & Smith, 1979; Rosenkranz *et al.*, 1980; Sanders, 1981; Ramdahl *et al.*, 1982; Butler *et al.*, 1983).

Several oxidized PAHs (e.g. ketones, quinones, anhydrides and carboxylic acids) were also identified in samples of carbon black that had undergone oxidative treatment (Fitch *et al.*, 1978; Fitch & Smith, 1979; Rivin & Smith, 1982), and one study detected 3-nitro-9-fluorenone in a nitric acid-treated carbon black that was used to make carbon ink in China (Jin *et al.*, 1987).

Carbon black that is made from high-sulfur feedstocks frequently contains detectable quantities of extractable aromatic compounds that contain sulfur such as benzothiophene derivatives (Lee & Hites, 1976; Nishioka *et al.*, 1986).

Trace amounts of a variety of inorganic elements (e.g. calcium, copper, iron, manganese, potassium, lead, arsenic, chromium, selenium and zinc) have also been identified in some analyses of samples of carbon black (Collyer, 1975; Sokhi *et al.*, 1990; Cabot Corporation, 2005b).

1.1.5 *Analysis*

This section briefly reviews methods for industrial hygiene measurements in workplaces where carbon black is manufactured or used, methods to detect the presence of carbon black in various matrices and methods used to isolate and analyse surface contaminants of carbon black (see Section 1.1.4).

(a) Industrial hygiene assessment

Exposure to particulates in occupational environments is generally determined gravimetrically. The behaviour of carbon black in air and its deposition in the respiratory

tract on inhalation are important for human exposure, and are determined by the aerodynamic diameter of the particles. The aerodynamic diameter can be measured by impactors and is dependent on the geometric diameter, density of the material and shape of the aggregates. Most commonly, the size distribution of airborne particles is expressed as its mass median aerodynamic diameter (MMAD) and the geometric standard deviation. Several dust fractions are often identified as 'total' dust, inhalable dust and respirable dust.

Inhalable dust is approximately equivalent to the fraction of airborne material that enters the nose and mouth during breathing and is therefore available for deposition anywhere in the respiratory tract (International Organization for Standardization, 1995; Health and Safety Executive, 2000). The inhalable fraction depends on the prevailing movement of air around the exposed person and on whether breathing is by the nose or mouth. It is, however, possible to define target specifications for sampling instruments which approximate the inhalable fraction; these target specifications are provided by the International Organization for Standardization (1995). In the United Kingdom, the standard sampling devices for measuring inhalable dust are the multiorifice sampler, the Institute of Occupational Medicine (IOM) sampler and the conical inhalable sampler (cis) (Health and Safety Executive, 2000).

Respirable dust is approximately equivalent to the fraction of the airborne material that penetrates the gas-exchange region of the lung. The respirable fraction varies for different individuals; however, it is possible to define a target specification for sampling instruments that approximates the respirable fraction for the average person (International Organization for Standardization, 1995). Respirable dust is generally collected using a cyclone pre-selector (Health and Safety Executive, 2000)

The term 'total' dust refers to the total particulate as represented (in North America at least) by the fraction that is collected by a closed-face three-piece plastic sampling cassette that holds a 37-mm filter (Eller, 1994; Occupational Safety and Health Administration, undated). The term 'total' dust is not equivalent to all airborne dust; in fact, measurements of inhalable dust using the IOM sampling head are 1.0–2.5 times higher than 'total' dust levels that are measured by a closed-face 37-mm filter cassette, depending on the aerodynamic diameter of the particle (Werner *et al.*, 1996).

Methods for the measurement of elemental carbon exist but have not been widely used in the carbon black manufacturing industry (e.g. Eller, 1994; Occupational Safety and Health Administration, undated). These are relatively complicated and expensive, but could be applied to environments in which mixed dust exposures exist, e.g. in tyre manufacture.

Recently, several studies have attempted to collect data on the size distribution of airborne particulates at carbon black manufacturing sites (Wake *et al.*, 2002; Kuhlbusch *et al.*, 2004;). This can be achieved by using a scanning mobility particle sizer (SMPS) linked to a condensation particle counter. The SMPS fractionates the particles that are in the size range of 15–734 nm through their electrical mobility. Kuhlbusch *et al.* (2004) also used an aerodynamic particle sizer to identify and characterize airborne particles with

CARBON BLACK 55

an aerodynamic diameter in the range of 0.5–15 μm by drawing the aerosol through a nozzle that accelerates the particles. The velocity of the particles is dependent upon their aerodynamic diameter (Kuhlbusch *et al.*, 2004).

The bioavailability of the PAHs adsorbed onto the surface of carbon black has been assessed by quantifying the concentration of the major adsorbed PAH, pyrene, using its urinary metabolite, 1-hydroxypyrene. The urine was adjusted to pH 5.0 and incubated with 50 μL β-glucuronidase/aryl sulfatase for 4 hours at 37 °C. After extraction and washing, the hydrolysed urine was injected into an HPLC unit with a fluorescence detector. The limit of detection was approximately 0.075 nmol/L [16 ng/L] (Gardiner *et al.*, 1992b). Similar methods have been reported more recently (Tsai *et al.*, 2002a).

(b) *Carbon black in various matrices*

Several organizations have published standard methods for the determination of carbon black in rubber (International Organization of Standardization, 1992; ASTM International, 2000 [D2663–95a]; Standards Australia International Ltd, 2001; ASTM International, 2003 [D6370–99], 2005b [D3192–05]). Standard methods for determining carbon black in polyolefin pipes and fittings are also available (International Organization for Standardization, 1986; ASTM International, 2001 [D4218–96]; Japanese Standards Association, 2003).

ASTM International (2004a) [D3849–04] has also published a method for the morphological characterization of carbon black primary aggregates by transmission electron microscopy to derive the mean particle and aggregate size of carbon black in the dry (as manufactured) state or in products. ASTM International (2004b) [D6602–03b] also has a method for distinguishing ASTM-type carbon black, in the N100 to N900 series, from other environmental particulates.

(c) *Adsorbates on carbon blacks*

Several methods have been reported for the extraction and analysis of adsorbates on carbon black. Soxhlet extraction with various organic solvents has been the primary method used to remove adsorbed chemicals from samples of carbon black, but vacuum sublimation or extraction combined with sonification have also been used (Zoccolillo *et al.*, 1984). The efficiency of Soxhlet extraction depends on extraction time and solvent, the type of carbon black, the relationship between weight of sample/volume of solvent and the amount of extractable material. Some solvents can react with the surface groups of carbon black and form artefacts during the extraction (Fitch *et al.*, 1978).

Taylor *et al.* (1980) examined the efficiency of three solvents (24-hour Soxhlet) as measured by extractability of benzo[*a*]pyrene from five furnace blacks. They found that toluene and benzene had quite similar efficiencies, but that cyclohexane could not remove more than 10% of the benzene-extractable benzo[*a*]pyrene from any of the furnace blacks. Toluene was, however, clearly the best extractant when the adsorbate content of the carbon black was low (less than 1 mg/kg).

Analytical methods used to determine the components of carbon black extracts produced by Soxhlet extraction with various solvents have been summarized (Jacob & Grimmer, 1979). Common methods include gas chromatography with packed and capillary columns and HPLC with spectrophotometric and spectrofluorometric detection.

Zoccolillo *et al.* (1984) reported the determination of PAHs in carbon black by Soxhlet extraction with benzene, purification by silica gel thin-layer chromatography and analysis by gas chromatography and/or HPLC.

Jin *et al.* (1987) described a method for the analysis of nitroarenes in carbon black which involved Soxhlet extraction of the sample with organic solvents (the use of chlorobenzene resulted in the highest overall yield), pre-separation by column chromatography on silica gel and separation and determination by reverse-phase HPLC with ultraviolet detection.

Several national and international organizations have published standard methods for the determination of total solvent-extractable material in carbon black and related products (International Organization for Standardization, 1988; Standards Australia International Ltd/Standards New Zealand, 2003; ASTM International, 2004c [D4527–99], ASTM International, 2005c [D305–84]). All methods involve Soxhlet extraction of the product with an appropriate solvent (acetone or toluene) and gravimetric determination of the extract residue after removal of the solvent.

1.2   Production and use

Carbon black is produced by the partial oxidation or thermal decomposition of hydrocarbon gases or liquids. Several processes have evolved over the years, yielding a variety of products that differ in particle size, structure, purity and method of manufacture, including furnace black, thermal black, lampblack, acetylene black and channel black. Furnace black is by far the predominant form of carbon black in commerce, and accounts for over 95% of total world production of carbon black. Thermal black is far less important and only minor quantities of the other three blacks are used in highly specialized applications. Approximately 70% the world consumption of carbon black is for the production of tyres and tyre products for automobiles and other vehicles. Approximately 20% is used in other rubber products such as hose, belting, mechanical and moulded goods, footwear and other uses, and the remainder (nearly 10%) is used in plastics, printing ink, paint, paper and miscellaneous applications (Auchter, 2005).

1.2.1   *Production*

(a)   *Processes*

Carbon black was first produced many centuries ago for use as a pigment in inks and lacquers by a simple lampblack process. The channel black process was developed in the nineteenth century when large quantities of natural gas became available, but worldwide use of carbon black was still less than 1000 tonnes. Following the discovery of the

usefulness of carbon black in the reinforcement of rubber at the beginning of the twentieth century, production increased rapidly and a gas-furnace process was introduced in the 1920s. In the 1940s, oil supplanted gas as a feedstock in the production of furnace black and, following the end of the Second World War, carbon black manufacture was established in many industrialized countries (Dannenberg *et al.*, 1992).

(i)   *Furnace black*

The oil-furnace process generates > 95% of all carbon black produced in the world. It was developed in 1943 and rapidly displaced previous gas-based technologies because of its higher yields and the broader range of carbon blacks that could be produced. It also captures particulates effectively and has greatly reduced their release into the environment around carbon black plants. The oil-furnace process is based on the partial combustion of residual aromatic oils. Because residual oils are widely available and are easily transported, the process can be carried out with little geographical limitation, which has led to the construction of carbon black plants all over the world. Plants are typically located in areas of tyre and rubber goods manufacture. Because carbon black has a relatively low density, it is far less expensive to transport feedstock than to transport the carbon black (Wang *et al.*, 2003).

The basic process consists of atomizing preheated oil in a combustion gas stream that is formed by burning fuel in preheated air. Some of the atomized feedstock is combusted with excess oxidant in the combustion gas. Temperatures in the region of carbon black formation range from 1400 to > 1800 °C. The gases that contain carbon black are quenched by spraying water into the stream as it passes through a heat exchanger and into a bag filter. The bag filter separates the unagglomerated carbon black from the by-product tail gas, which comprises mainly nitrogen and water vapour. The fluffy black from the bag filter is mixed with water to form wet granules that are dried in a rotary dryer and bagged or pelleted (Wang *et al.*, 2003).

Preferred feedstocks for the oil-furnace process are heavy fuel oils such as catalytic cracker residue (after removal of residual catalyst), ethylene cracker residues and distilled heavy coal-tar fractions. Other specifications of importance are absence of solid materials, moderate-to-low sulfur content and low alkali metal content (Wang *et al.*, 2003).

(ii)   *Thermal black*

Thermal black is made by the thermal decomposition of natural gas, coke-oven gas or liquid hydrocarbons in the absence of air or flames. Its economic production requires inexpensive natural gas. Today, it is among the most expensive of the carbon blacks that are regularly used in rubber goods. Because of its unique physical properties, it is used in some rubber and plastics applications such as O-rings and seals, hose, tyre inner liners, V-belts, other mechanical goods and in cross-linked polyethylene for electrical cables (Wang *et al.*, 2003).

The thermal black process, which dates from 1922, is cyclic and uses two refractory-lined cylindrical furnaces or generators. While one generator is heated to about 1300 °C

with a burning mixture of air and hydrogen off-gas, the other pre-heated generator is fed with natural gas which 'cracks' to form carbon black and hydrogen. The effluent gas, which comprises approximately 90% hydrogen, carries the carbon black to a quench tower where water sprays lower its temperature before it enters the bag filter. The carbon black collected from the filters is screened, hammer-milled and then bagged or pelleted (Wang *et al.*, 2003).

(iii)   *Lampblack*

The lampblack process is the oldest and most primitive carbon black process that is still being carried out. The ancient Egyptians and Chinese employed techniques similar to modern methods that collect the lampblack by deposition on cool surfaces. Basically, the process consists of burning various liquid or molten raw materials in large, open, shallow pans under brick-lined flue enclosures with a restricted air supply. The smoke from the burning pans passes through low-velocity settling chambers from which the carbon black is cleared by motor-driven ploughs. In more modern installations, the carbon black is separated by cyclones and filters. Lampblacks have similar properties to the small-surface area oil-furnace blacks. Production is small, and is mostly carried out in Europe. The main use of lampblack is in paints, as a tinting pigment in which a blue tone is desired and in some special applications in the rubber industry (Wang *et al.*, 2003).

(iv)   *Acetylene black*

The high carbon content of acetylene (92%) and its exothermic decomposition to carbon and hydrogen make it an attractive raw material for conversion to carbon black. Acetylene black is made by a continuous decomposition process at atmospheric pressure and 800–1000 °C. Acetylene is fed into reactors where, at temperatures above 800 °C, the exothermic reaction is self-sustaining and requires cooling by water to maintain a constant reaction temperature. The carbon black-laden hydrogen stream is then cooled followed by separation of the carbon from the hydrogen tail gas. Acetylene black is very fluffy with a bulk density of only 19 kg/m^3, is difficult to compact and resists pelletization. Commercial grades are compressed to various bulk densities of up to 200 kg/m^3. The unique features of acetylene black result in high electrical and thermal conductivity, low moisture adsorption and high liquid absorption (Wang *et al.*, 2003).

(v)   *Channel black*

Between the First and the Second World Wars, the channel black process produced most of the carbon black used worldwide for rubber and pigment applications. The last channel black plant in the USA was closed in 1976. The demise of channel black was caused by environmental problems, cost, smoke pollution and the rapid development of oil-furnace process grades that were equal or superior to channel black products, particularly for use in synthetic rubber tyres (Wang *et al.*, 2003).

The name channel black derived from the steel channel irons used to collect carbon black deposited by small flames of natural gas that impinged on their surface iron channels. Today, coal-tar fractions are used as raw material in addition to natural gas and,

in modern installations, channels have been replaced by water-cooled rollers. The carbon black is scraped off the rollers, and the off-gases from the steel box-enclosed rollers are passed through bag filters where additional carbon black is collected. The oils used in this process must be vapourized and conveyed to the large number of small burners by means of a combustible carrier gas, such as coke-oven gas. The yield of rubber-grade carbon black is 60% and that of high-quality colour grades is 10–30%. The characteristics of carbon blacks from roller process impingement are basically similar to those of channel blacks. The grades of smaller particle size are used as colour (pigment) carbon blacks and the larger (~30 nm) grade is used in rubber (Wang *et al.*, 2003).

(b) Capacity, production and consumption of carbon black

Carbon black is produced worldwide. Table 1.8 presents world capacity for carbon black production.

The consumption of carbon black in western Europe over the past decade rose to 1509 thousand tonnes in 2000 but has steadily declined since then to 1397 thousand tonnes in 2004. Production capacities were sharply reduced during this time of lower demand, from 1455 thousand tonnes in 2000 to 1273 thousand tonnes in 2004 (see Table 1.9) (Auchter, 2005).

Trends in production of carbon black in central and eastern European countries over a similar time period are presented in Table 1.10.

As in western Europe, consumption (and also production and capacity) of carbon black in the USA peaked in 2000. Table 1.11 provides an overview of carbon black supply and demand in the USA since 1971. There are currently five producers of furnace black in the USA, one of which also makes thermal black. In addition, two manufacture bone black and another produces lampblack (Auchter, 2005).

There are eight producers of carbon black in Japan; the seven producers of furnace black represent 97% of total capacity and one company produces acetylene black. Japanese supply of and demand for carbon black since 1991 are summarized in Table 1.12.

Annual capacity of producers of carbon black in other countries in Asia and the East (as of January 2005) was estimated to be 3.25 million tonnes, including Australia (87 000 tonnes), China (1 381 000 tonnes), India (584 000 tonnes), Indonesia (135 000 tonnes), Malaysia (100 000 tonnes), the Philippines (1000 tonnes), Republic of Korea (620 000 tonnes), Singapore (12 000 tonnes), Taiwan, China (110 000 tonnes) and Thailand (220 000 tonnes) (Auchter, 2005).

1.2.2 *Use*

The primary use of carbon black is in rubber products, particularly in tyres, but also in many other automotive and non-automotive rubber applications. Carbon black also is used in paint, plastics, paper, inks, ceramics and other minor applications. Consumption patterns in the USA, western Europe and Japan in 2004 are summarized in Table 1.13.

60   IARC MONOGRAPHS VOLUME 93

Table 1.8. World capacity for carbon black production (as at 1 January 2005)

Region	Million tonnes	Percentage of total
North America[a]	2.3	25
South America	0.5	6
Western Europe	1.3	14
Eastern Europe	1.4	16
Japan	0.8	9
Other Asia[b]	3.3	26
Africa and Middle East	0.4	4
Total	10.0	100

From Auchter (2005)
[a] Canada, Mexico and the USA
[b] Australia, China, India, Indonesia, Malaysia, the Philippines, Republic of Korea, Singapore and Thailand

Table 1.9. Western European production capacity for carbon black (as at 1 January 2005)

Country	No. of plants	Thousand tonnes	Percentage
Belgium	1	6	<1
France	4	264	21
Germany	4	322	25
Italy	3	221	17
Netherlands	2	155	12
Portugal	1	35	3
Spain	1	60	5
Sweden	1	40	3
United Kingdom	2	170	13
Total	19	1273	100

From Auchter (2005)

CARBON BLACK 61

Table 1.10. Central and eastern European production of carbon black (thousand tonnes)

Year	Croatia	Czech Republic	Hungary	Poland	Romania	Russia	Other[a]	Total
1994	22	41	42	26	19	350	40	540
1997	24	53	50	25	21	316	25	514
2000	21	65	50	24	13	425	23	621
2002	20	80	50	26	16	529	26	747
2004	25	95	50	19	18	670	20	897

From Auchter (2005)
[a] Mainly Slovakia and the Ukraine

Table 1.11. Capacity, production and consumption of carbon black in the USA (thousand tonnes)[a]

Year	No. of operating plants	Capacity	Production	Consumption
1971	42	1820	1380	1295
1981	35	1575	1285	1200
1991	21	1538	1216	1195
1994	21	1635	1501	1505
1997	21	1889	1592	1592
2000	21	2020	1642	1670
2004	18	1847	1617	1592

From Auchter (2005)
[a] Includes furnace black, thermal black, acetylene black, bone black and lampblack

Table 1.12. Japanese capacity, production and consumption of carbon black (thousand tonnes)

Year	Capacity	Production	Consumption
1991	788	793	796
1994	785	704	714
1997	845	776	828
2000	787	767	828
2004	751	804	872

From Auchter (2005)

Table 1.13. Consumption patterns of carbon black in 2004 (thousand tonnes)

Use	USA	Western Europe	Japan
Automotive use			
Tyres, tubes and tread	1098	936	655
Belts, hoses and miscellaneous	159		
Other rubber products (industrial, molded and extruded goods)	145	335	170
Non-rubber use (paint, plastics, paper, ink, ceramics and other)	191	126	47
Total	1593	1397	872

From Auchter (2005)

Carbon black is used to reinforce rubber—that is, to increase the resistance of rubber to abrasion, tear, fatigue and flexing. It also improves the tensile strength and processing characteristics of many elastomers (natural and synthetic). Consumption of carbon black worldwide is highly dependent on the rubber industry, which typically accounts for 89–91% of total consumption (Auchter, 2005).

The major use for carbon black in elastomers is in tyre manufacture (automobile, truck, bus, agricultural, aircraft and industrial), retread rubber and inner tubes. Carbon black typically comprises 20–40% of the tyre by weight. Other automotive applications of carbon black include its use in elastomers for wire and cable, belts, hoses, O-rings, insulation stripping, shock and motor mounts and other such products. Carbon black is used in elastomers in applications other than automotive, including hoses, conveyor belts, roofing, covers for wire and cable, coated fabrics, gaskets, packaging, gloves, footwear, floor mats, tape, hard rubber products, pontoons and toys (Auchter, 2005).

Plastics are the largest non-elastomer use for carbon black. In addition to use as a colourant, carbon black is frequently used as an effective stabilizer of ultraviolet light, an additive for controlling electrical conductivity or a strength-imparting filler.

The printing ink industry consumes almost one-third of the special industrial (non-rubber) carbon blacks produced in the USA. The grade and concentration used depend on the type and quality of the ink and are selected for factors such as the required degree of colour, gloss, tone, viscosity, tack and rheological properties. Carbon black content of inks ranges from 5 to 22%.

Carbon black is used as a colourant for tinting and pigmentation in all types of paints and coatings. Relatively small quantities are added to some industrial formulations (e.g. primers and floor finishes) to impart electrical conductivity.

The production of carbon paper is the principal use of carbon black in the paper industry. Other uses are in photograph albums, leatherboard, wrapping and bag papers, in backing paper for photographic film and in highly conductive and electrosensitive papers.

Miscellaneous other applications of carbon black are in dry-cell batteries, photocopy toners and magnetic tapes (Auchter, 2005).

1.3   Occurrence

1.3.1   *Natural occurrence*

Carbon black does not occur as a natural product.

1.3.2   *Occupational exposure*

Human exposure is primarily to the aggregate and agglomerate forms of carbon black.

A large amount of data on exposure to carbon black is available from surveys conducted in the carbon black manufacturing industry in Europe and the USA. Much less is known on exposure to carbon black in downstream user industries, most notably the rubber industries. In these industries, carbon black is often only one of many substances being used and its specific measurement has rarely been taken. Measurements of occupational exposure to particulates are generally taken using non-specific dust sampling methods, as described in Section 1.1.5(*a*). For the carbon black manufacturing industry, the assumption can be made that carbon black particles are predominantly measured by these sampling devices (Kuhlbusch *et al.*, 2004). Other important issues in a review of occupational exposure to carbon black are the physical and chemical characteristics of the particles. Generally, very little is known about the levels of ultrafine carbon black in manufacturing and downstream user industries.

The National Occupational Exposure Survey conducted in the USA by the National Institute for Occupational Safety and Health (1995) between 1981 and 1983 indicated that about 1 729 000 employees were potentially exposed to carbon black. [The estimate is based on a survey of companies and did not involve measurements of actual exposure, and might, for many workers, involve very low levels and/or incidental exposure to carbon black.]

No data were available on exposure to carbon black in the non-automotive rubber, paint, printing or printing ink (i.e. 'user') industries. Operators in user industries who handle fluffy or pelleted carbon black during rubber, paint and ink production are expected to have significantly lower exposures to carbon black than workers in carbon black production. Other workers in user industries who handle it occasionally have little opportunity for exposure. End-users of these products (rubber, ink or paint) are unlikely to be exposed to airborne carbon black particles, which are bound within the product matrix.

(a) Manufacturing industries

The results of two large-scale multiphase industry-wide exposure assessment surveys in Europe and the USA are summarized below, followed by a review of results from smaller and often older studies. In the European study, exposures to inhalable and respirable dust were measured. Levels of exposure to carbon black in the carbon black manufacturing industry in the USA have been expressed as 'total' or respirable dust and, more recently, as inhalable dust. A study by Kerr *et al.* (2002) investigated the relationship between inhalable dust (using the IOM sampling head) and 'total' dust (using 37-mm closed cassettes) and found a ratio of 2.97 (inhalable:total) which can be used to convert 'total exposure' into inhalable dust exposure, as performed by Harber *et al.* (2003) for the data from the USA.

(i) Major surveys conducted in Europe

A large study of the respiratory health effects of exposure to carbon black dust was carried out in the European carbon black manufacturing industry (Gardiner *et al.*, 1993, 2001; van Tongeren *et al.*, 2002). As part of this study, a large quantity of exposure data was collected during three surveys (survey I, 1987–89; survey II, 1991–92; and survey III, 1994–95) in 18 factories in seven countries across western Europe (France, Germany, Italy, the Netherlands, Spain, Sweden, United Kingdom) (Gardiner *et al.*, 1992a, 1996; van Tongeren, 2000; van Tongeren *et al.*, 2000). Both respirable and inhalable dust fractions were measured, and a total of 8015 inhalable and 7404 respirable measurements were collected from a large proportion of the workforce. Tables 1.14 and 1.15 present the results of exposure measurements of inhalable and respirable dust by occupational category, respectively.

The highest exposure levels were observed for warehousemen, who are responsible for the packing and shipment of carbon black, and the site crew, who are responsible for cleaning any carbon black spillages. The arithmetic mean exposure to inhalable dust for the warehousemen was reduced from 3.4 mg/m^3 in the first survey to 1.7 mg/m^3 in the second and 1.5 mg/m^3 in the third survey. Similar declining trends were observed for other occupational categories (van Tongeren, 2000; van Tongeren *et al.*, 2000).

van Tongeren (2000) calculated the probability that the long-term mean exposure of a worker's to inhalable dust is in excess of the occupational exposure limit of 3.5 mg/m^3 and found that, for warehousemen, this probability declined from 42% in the first survey to 9% in the second and to only 4% in the third survey. For the site crew, these probabilities were 21%, 10% and 10%, respectively. Personal exposure levels varied significantly across the various factories, even within the same job category.

As the mortality studies in Europe were carried out in the United Kingdom and Germany, the levels of exposure to inhalable dust for the packers (warehousemen) in factories in these countries have been presented in Table 1.16. The results suggest that there is considerable variation in exposure between the factories. For example, in the first survey (1987–89), exposure to inhalable dust varied from 0.1 mg/m^3 in one German factory to 6 mg/m^3 in another German factory. The exposure levels for the warehouseman

Table 1.14. Exposure measurements of inhalable dust (mg/m^3) by job category and survey in the European carbon black manufacturing industry

Job category	Survey I (1987–89)					Survey II (1991–92)					Survey III (1994–95)				
	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range
Administrative staff	313	0.26	0.16	2.63	0.02–3.55	516	0.27	0.15	3.00	0.02–7.46	571	0.24	0.11	3.10	0.02–7.35
Laboratory staff/ process control room operator	192	0.60	0.32	2.91	0.02–10.15	514	0.37	0.23	2.82	0.02–4.58	491	0.32	0.18	2.95	0.02–4.88
Instrument mechanic/ electrician	111	1.37	0.54	3.62	0.02–26.83	437	0.63	0.37	2.99	0.02–8.61	284	0.49	0.28	2.99	0.02–11.31
Process foreman/ furnace operator	169	0.91	0.49	3.11	0.02–10.29	491	0.57	0.30	3.38	0.02–9.49	489	0.53	0.28	3.31	0.02–8.07
Fitter/welder	139	1.66	1.01	2.81	0.02–19.63	358	1.08	0.62	3.27	0.02–8.75	420	0.87	0.49	3.15	0.02–9.39
Process/conveyor operator	205	1.67	0.71	3.58	0.02–26.51	532	0.93	0.52	3.17	0.02–16.92	411	0.66	0.36	3.14	0.02–14.36
Warehouseman	155	3.35	1.69	3.65	0.02–35.44	455	1.68	0.88	3.44	0.02–19.95	428	1.52	0.84	2.98	0.02–37.28
Site crew	32	3.72	1.24	4.62	0.13–18.25	151	1.33	0.60	3.57	0.02–18.07	151	1.17	0.51	3.97	0.02–12.53
Total[a]	1316	1.30	0.48	3.96	0.02–35.44	3454	0.79	0.37	3.60	0.02–19.95	3245	0.67	0.29	3.68	0.02–37.28

Adapted from van Tongeren (2000)

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements

[a] Summary of results of all measurements (not mean of means)

Table 1.15. Exposure measurements of respirable (mg/m³) dust by job category and survey in the European carbon black manufacturing industry

Job category	Survey I (1987–89)					Survey II (1991–92)					Survey III (1994–95)				
	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range	No.	AM	GM	GSD	Range
Administrative staff	299	0.24	0.14	2.28	0.02–9.31	497	0.19	0.11	2.74	0.02–5.28	525	0.17	0.08	2.88	0.02–4.32
Laboratory staff/process control room operator	185	0.22	0.16	2.20	0.02–2.47	497	0.20	0.13	2.56	0.02–3.65	522	0.18	0.10	2.78	0.02–2.91
Instrument mechanic/electrician	118	0.33	0.20	2.51	0.02–6.54	302	0.37	0.17	2.89	0.02–24.65	314	0.21	0.12	2.61	0.02–2.49
Process foreman/furnace operator	153	0.31	0.21	2.36	0.02–4.81	406	0.34	0.19	2.80	0.02–4.16	470	0.22	0.12	2.96	0.02–3.68
Fitter/welder	144	0.42	0.29	2.42	0.02–4.11	294	0.39	0.21	2.95	0.02–7.71	361	0.28	0.15	2.92	0.02–3.55
Process/conveyor operator	200	0.54	0.24	2.83	0.02–16.69	389	0.35	0.19	3.04	0.02–3.35	396	0.34	0.17	3.16	0.02–4.41
Warehouseman	161	0.82	0.44	2.90	0.02–12.00	394	0.69	0.34	3.02	0.02–18.99	394	0.54	0.28	3.18	0.02–6.23
Site crew	37	0.66	0.29	3.42	0.02–7.41	171	0.55	0.26	3.03	0.02–20.70	175	0.49	0.18	4.00	0.02–6.60
Total[a]	1297	0.40	0.21	2.69	0.02–16.69	2950	0.36	0.18	2.46	0.02–24.65	3157	0.28	0.13	3.17	0.02–6.60

Adapted from van Tongeren (2000)

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements

[a] Summary of results of all measurements (not mean of means)

Table 1.16. Exposure of warehousemen to inhalable dust (mg/m^3) in factories the United Kingdom and Germany

Country	Factory	1987–89				1991–92				1993–95			
		No.	AM	GM	GSD	No.	AM	GM	GSD	No.	AM	GM	GSD
United Kingdom	1	10	3.50	1.71	3.91	30	2.68	1.51	3.83	53	3.47	1.77	3.4
	2	14	3.26	1.62	4.03	31	1.24	0.8	2.64	38	0.66	0.46	2.75
Germany	6	11	2.76	1.47	5.04	43	1.78	1.04	3.57	44	2.71	1.29	3.37
	7	4	0.11	0.06	3.94	11	0.36	0.2	4				
	8	4	0.62	0.47	2.29	14	0.84	0.59	2.98				
	9	11	6.02	3.31	3.51	34	2.17	1.71	1.95	20	1.44	1.10	2.42
	10	6	1.94	1.75	1.66	50	2.13	0.84	3.82	62	1.01	0.65	3.08

Adapted from van Tongeren (2000)

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; No., number of measurements

CARBON BLACK

in this German factory fell over time to 1.44 mg/m^3 in 1993–95. Exposure in factories in the United Kingdom was between 3 and 3.5 mg/m^3 in 1987–89; however, while the exposure among the warehousemen in one factory declined to approximately 0.7 mg/m^3 in 1993–95, exposure in the other factory remained relatively stable.

(ii)   *Major surveys in the USA*

Five industry-wide exposure surveys were conducted in the USA (Harber *et al.*, 2003) in 1979 (Smith & Musch, 1982), 1982–83 (Musch & Smith, 1990), 1987 (Musch & Smith, 1990), 1993–95 (Muranko *et al.*, 2001) and 2000–01 (unpublished).

In the first survey, a total of 1951 personal samples (1564 'total' dust, 387 respirable dust) were collected from 24 carbon black production facilities in the USA (Smith & Musch, 1982). A summary of the results are provided in Table 1.17. Workers who were involved in filling and stacking bags of carbon black (material handling) had the highest mean exposures to 'total' dust of up to 2.2 mg/m^3. Samples were not taken from all employment areas in every factory and the numbers of samples taken differed from area to area.

Table 1.17. Average dust exposure by employment area in carbon black production facilities in the USA (1979–80)

Area of employment	'Total' dust			Respirable dust		
	No. of plants	No. of samples	GM (mg/m^3)	No. of plants	No. of samples	GM (mg/m^3)
Administration	8	72	0.01	2	28	0.00
Laboratory	17	133	0.04	10	35	0.01
Production	22	480	0.44	14	111	0.13
Maintenance	19	386	0.59	11	89	0.12
Material handling	20	493	1.45	13	124	0.35

From Smith & Musch (1982)
GM, geometric mean

The particulate sampling survey of 1979–80 (Smith & Musch, 1982) was conducted again in 1980–82 and in 1987 (Musch & Smith, 1990). The number of participating companies decreased from seven to six and the number of plants decreased from 24 to 17. In 1980–82, 973 'total' dust samples were taken; the number fell to 577 in 1987. The data are summarized in Table 1.18. A drop of approximately 50% in exposure was evident in maintenance and material-handling sectors of the factories. Of the job categories in the maintenance sector, the following reductions were seen between the second and third surveys: utility, 0.89 down to 0.55 mg/m^3; inplant, 0.79 down to 0.52 mg/m^3; shop, 1.00 down to 0.07 mg/m^3; instrument, 0.47 down to 0.17 mg/m^3; and foreman, 0.35 down to 0.18 mg/m^3. Of the job categories in the material-handling sector, the following

reductions were seen between the second and third surveys: stack and bag, 1.92 down to 0.77 mg/m^3; bagger, 2.67 down to 0.85 mg/m^3; bulk loader, 2.07 down to 0.82 mg/m^3; stacker, 1.15 down to 0.70 mg/m^3; fork-lift truck driver, 0.53 down to 0.34 mg/m^3; and foreman, 0.18 down to 0.02 mg/m^3.

Table 1.18. Average exposure to 'total' dust by employment area in carbon black production facilities in the USA in 1980–82 and 1987

Area of employment	1980–82		1987	
	No. of samples	GM (mg/m^3)	No. of samples	GM (mg/m^3)
Administration	4	0.06	2	0.02
Laboratory	85	0.51	23	0.20
Production	273	0.45	164	0.45
Maintenance	363	0.71	181	0.36
Material handling	248	1.63	207	0.71

From Musch & Smith (1990)
GM, geometric mean

A later industry-wide survey was carried out between 1993 and 1995, during which period 1004 'total' and 1056 respirable dust measurements were collected from 21 plants from seven companies (Muranko *et al.*, 2001). The results of these measurements are summarized in Table 1.19. Results indicated that exposure had declined since the previous studies. Highest exposure levels to 'total' dust were observed for material handling; respirable dust levels were much lower. Results from 680 matched pairs of respirable and 'total' samples found a mean ratio of 0.37 (respirable:'total').

A survey was carried out in 2000–01 to measure exposure to inhalable and respirable dust in 22 plants from seven different carbon black manufacturing companies. No further details were available, although a summary of exposure to inhalable dust only by job category from this survey has been published (Harber *et al.*, 2003) (Table 1.20).

Using the conversion factor provided by Kerr *et al.* (2002), the results from the 'total' dust measurements were converted into inhalable dust (Harber *et al.*, 2003). Table 1.20 shows the estimated levels of exposure to inhalable dust by job category and sampling survey. In the early surveys, only geometric means (GMs) were reported. The levels of exposure to inhalable dust (GM) during the handling of materials declined from 4.31 mg/m^3 and 4.84 mg/m^3 in the first and second surveys to 2.11 mg/m^3, 1.13 mg/m^3 and 1.57 mg/m^3 in the third, fourth and fifth surveys, respectively. Levels of exposure in other job categories were lower in all of the surveys, although the arithmetic mean exposure in production in 1987 was higher than that in materials handling (7.70 mg/m^3 versus 6.40 mg/m^3).

Table 1.19. Levels of exposure to 'total' and respirable dust (mg/m^3) in the carbon black manufacturing industry in the USA, 1993–95

	No. of samples	AM	GM	GSD	Range	% >OEL
'Total'						
Administration	0					
Laboratory	144	0.30	0.14	3.55	0.01–2.59	0.5
Production	321	0.41	0.14	4.38	0.01–13.25	1.5
Maintenance	289	0.50	0.22	3.66	0.01–9.66	1.6
Material Handling	250	1.16	0.38	4.51	0.01–12.05	6.9
All	1004	0.59	0.20	4.31	0.01–13.25	2.6
Respirable						
Administration	0					
Laboratory	146	0.08	0.05	2.94	0.01–0.80	–
Production	321	0.11	0.05	3.36	0.01–2.62	–
Maintenance	323	0.14	0.07	3.35	0.01–1.41	–
Material Handling	266	0.23	0.11	3.38	0.01–2.31	–
All	1056	0.15	0.07	3.45	0.01–2.62	–

From Muranko *et al.* (2001)
AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; OEL, observed effect level

(iii)   *Other studies*

Kollo (1960) took 160 measurements in a Russian channel black plant where airborne dust levels ranged from 44 to 407 mg/m^3 in the factory area, from 25.3 to 278.6 mg/m^3 in the working aisles, from 9.3 to 972 mg/m^3 in the pelleting area and from 26.7 to 208.6 mg/m^3 in the packing area.

Komarova (1965) measured exposure to carbon black in the packaging departments of two Russian factories that manufactured lampblack and furnace black. The number of measurements was not specified, but the ranges were 166–1000 mg/m^3 (lampblack) and 60–78 mg/m^3 (furnace black). Slepicka *et al.* (1970) found exposures ranging from 8.4 to 29.0 mg/m^3 in two Czechoslovakian channel black factories between 1960 and 1968, although neither the number of samples nor their location were reported.

A survey in a Russian furnace black factory found a range of concentrations of 90–196 mg/m^3 [number of samples unspecified] (Spodin, 1973). The lowest and highest average concentrations recorded by another Russian factory were 1.53 ± 0.4 mg/m^3 for workers by the hatches of the electrostatic filter and 34.5 ± 8.9 mg/m^3 for workers involved in cleaning the production areas; in total, 109 samples were taken. It was noted that throughout the 1960s and 1970s, workers who packed carbon black were exposed to

Table 1.20. Exposure to inhalable dust (measured or converted from 'total' dust; mg/m^3) by job category and survey in the carbon black manufacturing industry in the USA

	1979–80			1980–82			1987			1993–95			2000–01		
	No.	AM	GM	No.	AM	GM	No.	AM	GM	No.	AM	GM	No.	AM	GM
Administration	72	NA	0.03	4	NA	0.18	2	0.53	0.06	0	–	–	125	0.35	0.18
Laboratory	133	NA	0.12	85	NA	1.51	23	3.15	0.59	144	0.89	0.59	103	0.86	0.44
Production	480	NA	1.31	273	NA	1.34	164	7.70	1.34	321	1.22	0.42	273	1.18	0.47
Maintenance	386	NA	1.75	363	NA	2.11	181	3.62	1.07	289	1.49	0.65	257	1.34	0.66
Materials handling	493	NA	4.31	248	NA	4.84	207	6.40	2.11	250	3.45	1.13	247	2.70	1.57

From Harber *et al.* (2003)
AM, arithmetic mean; GM, geometric mean; NA, not available; No., number of measurements
For 1979, 1983, 1987 and 1995 'total' dust levels were converted to inhalable dust levels based on a 2.97:1.0 ratio for inhalable: 'total'.
The estimated GM for laboratory in 1995 appears to be incorrect when compared with the original data.

CARBON BLACK

two to seven times the maximal permissible concentration (10 mg/m^3 in 1975) for 60–70% of their working shifts (Troitskaya *et al.*, 1975, 1980).

In a mortality study conducted in the United Kingdom (Hodgson & Jones, 1985), a limited amount of exposure data had been collected by Her Majesty's Factory Inspectorate in 1976. Personal samples were taken from 47 people in five carbon black factories; 24 (51%) of the samples were > 3.5 mg/m^3. The highest exposure recorded for routine work was 79 mg/m^3, but workers engaged in filter-bag replacement may have been exposed to even higher levels, although exposure measurements were not reported.

In a small study to determine the bioavailability of adsorbed PAHs, Gardiner *et al.* (1992b) measured exposure to inhalable dust for five individuals who packed carbon black into 25-kg bags over a 1-week period. Personal mean dust exposures were 1.53, 5.30, 9.56, 9.99 and 13.21 mg/m^3.

Szozda (1994) reported some exposure levels based on measurements in three Polish carbon black manufacturing plants. Concentrations of total dust varied from < 10 mg/m^3 to 28.51 mg/m^3, although levels of up to 81.26 mg/m^3 were found in the packing department. Levels of carbon black in the same facilities were reported to range between 0.62 mg/m^3 and 60.61 mg/m^3, although levels in the packing department could reach up to 73.34 mg/m^3 with incidental levels of 675.5 mg/m^3. [No method for the measurement of total dust and carbon black was provided, and it is not clear what is meant by the various ranges in exposure. The result does, however, suggest that the exposure levels in these Polish carbon black manufacturing plants are higher than those in the USA and western Europe.]

(iv) *International comparison and trends over time*

It is feasible that levels of exposure to carbon black differ between workers who are employed only in the furnace process and those who are employed in other production processes (either exclusively or in addition to the furnace process). Unfortunately, the data from studies in western Europe and the USA do not allow analyses by process, and hence no objective information is available to confirm this.

A comparison of exposure surveys in Europe and the USA (Tables 1.14 and 1.20) that were carried out between the late 1980s and mid-1990s suggest that, at least for levels of inhalable dust, exposure was somewhat higher in the USA than in western Europe. For example, the overall arithmetic exposure to inhalable dust for the warehouseman in the western European study varied from 3.35 mg/m^3 in 1987–89 to 1.52 mg/m^3 in 1993–95 compared with 6.40 mg/m^3 (1987) and 3.45 mg/m^3 (1994–95) for materials handling in the study in the USA. In contrast, levels of exposure to respirable dust in the USA were lower than those in western European factories (Tables 1.15 and 1.19). These apparently contradictory results may indicate that the conversion factor (2.97) used in the studies to convert 'total' to inhalable dust levels in the USA may have been too high.

Werner *et al.* (1996) also compared the inhalable and 'total' dust fractions and observed lower inhalable:'total' dust ratios. It is possible that the application of one conversion factor for all exposure levels in every part of the process and each factory may

lead to erroneous results, as the inhalable:'total' dust ratio depends on particle size, which probably varies between factories and stages in the process. In addition, in the European study, only the filters were analysed gravimetrically rather than the whole IOM cassette, as is standard practice. This was due to external contamination of the cassettes, and could have resulted in an underestimation of the European levels by a factor of up to 20% (Gardiner *et al.*, 1992a,c).

The available data on exposure in the carbon black manufacturing industry suggest that levels have been declining since the 1960s and 1970s. Van Tongeren *et al.* (2000) analysed the data from the European carbon black manufacturing industry and found statistically significant reductions in inhalable dust exposure levels between the first (1987–89) and third (1994–95) survey, ranging from approximately a 30% reduction (GM) for the administrative staff to nearly a 60% reduction for the warehousemen and site crew. In the USA, exposure levels in warehouse operations decreased by more than 50% (GM) between 1979 and 1987 and by an additional 25% (GM) between 1987 and 2000, while significant declines occurred between 1987 and 2000 in production (AM, 85%; GM, 65%) and maintenance (AM, 63%; GM, 38%) (Harber *et al.*, 2003).

A retrospective exposure assessment was carried out for the two carbon black producing factories in the United Kingdom, which was used for the mortality study of the carbon black workers (Sorahan *et al.*, 2001). The retrospective exposure estimates were based on information provided by the companies, including exposure data, production rates and process changes. Levels of exposure to inhalable dust in the 1950s were estimated to be approximately 20 mg/m^3 for warehousemen and 30 mg/m^3 for cleaning staff (non-office). [The Working Group noted that these estimates were predominantly based on estimated effects of changes in production or control measures rather than on quantitative data, and should therefore be interpreted with caution.]

It is probable that the reduction in exposure is caused mainly by changes in the process, technological improvements, increases in the proportion of the product that is bulk loaded (by trucks and trains), hygiene and cleaning regimes, and legislative enforcement (Harber *et al.*, 2003). [Some of the decline in exposure may also have been the result of outsourcing heavily exposed tasks to other companies or contractors. Even when they had worked at the carbon black manufacturing facilities for long periods of time, contractors were not generally included in the exposure studies.]

(v)   *Particle size distribution*

Little is known about the size distribution of airborne particles in the carbon black manufacturing industry. Measurements of respirable and inhalable dust have been carried out in the studies in Europe and the USA. In the European study, the respirable dust fraction of the inhalable dust ranged between 0.31 and 0.46; however, in the study in the USA, the respirable dust fraction appeared to be much lower: 0.17 in 2001 and 0.09 in 1993–95 (based on estimated levels of inhalable dust).

Two studies investigated the levels of ultrafine particles at carbon black manufacting sites (Wake *et al.*, 2002; Kuhlbusch *et al.*, 2004).

Kuhlbusch *et al.* (2004) took measurements in the packing areas of three carbon black manufacturing facilities using an SMPS and an aerodynamic particle sizer. Particle number concentrations were determined for three classes of size which correspond to three particle modes: nucleation mode (10–100 nm), accumulation mode (200–700 nm) and coarse mode (1–10 μm). Comparable results were obtained from the three plants and showed two particle modes. During bag filling, the particle number concentrations increased for particles > 400 nm aerodynamic diameter with modes of around 1 μm and > 8 μm. Ultrafine particle emissions (< 100 nm aerodynamic diameter) detected in the bag-filling areas could be attributed to forklifts running either on propane or diesel. Another source of ultrafine particles could be butane gas heaters in one of the plants.

The study by Wake *et al.* (2002) used an SMPS to estimate the total number of particles with a diameter between 16.5 and 805 nm inside (bagging) and outside a carbon manufacturing facility. The particle count in the bagging plant was much lower than that measured outside, which was probably due to particles emitted from road vehicles. Compared with other processes, the levels were similar to those found during bagging activities in nickel powder production, titanium dioxide production and plasma coating, but much lower than those found in a steel foundry and near a welding or plastic welding process.

(vi)   *Exposure to PAHs*

The retention of particles in the lungs may influence the bioavailability of adsorbed materials. As the retention of particles increases, the potential for adsorbed PAHs to be eluted and absorbed may also increase.

In a study of five nonsmoking warehouse packers in a carbon black (furnace black) manufacturing plant, daily average exposures to dust were measured by air sampling, and urinary excretion of 1-hydroxypyrene (derived from pyrene) was measured in post-shift urine samples for five consecutive days during one work week. The mean ambient dust concentrations over the five days ranged from 1.5 to 13 mg/m^3. Excretion of 1-hydroxypyrene ranged from 0.10 to 0.48 μmol/mol creatinine. A regression model showed a statistically significant relationship between weekly mean concentration of airborne dust and excretion of 1-hydroxypyrene (when assuming zero excretion of 1-hydroxypyrene with zero measured dust exposure). Urinary excretion of 1-hydroxypyrene was statistically significantly lower on Monday than on other days; the authors concluded that this was affected by exposure to dust, and that the pyrene on the dust was bioavailable (Gardiner *et al.*, 1992b). [The Working Group noted that the pyrene content of the carbon black was not measured; the airborne sampling method and particle size distribution were not described. Rather than performing regression analyses based on the mean exposures of individuals for the week, it may be more informative to use the daily values of individuals in a mixed model that accounts for correlation within each of the individual values. Also, using a lag could be informative to account for the time between dust inhalation, pyrene metabolism and 1-hydroxypyrene elimination.]

Levels of particle-bound and gaseous PAHs were determined in a carbon black manufacturing plant in southern Taiwan, China (China) from personal and stationary measurements (Tsai *et al.*, 2002a,b). Dermal exposure was also determined in a small number of workers. Results for gaseous and particle-bound PAHs are shown in Table 1.21 and suggest that levels of total particle-bound and gaseous-phase PAHs were approximately equal. These are somewhat in contrast to the results from stationary measurements in eight production areas in the same carbon black plant (Table 1.22), which showed that less than 3% of total PAHs were particle-bound in all areas except for the packing area, where 31% of the total PAHs was particle-bound (Tsai *et al.*, 2002b).

From the same factory in Taiwan, China (China), urinary samples were obtained from eight pelleting workers and 22 packers on day 1 pre-shift, day 1 post-shift and day 5 post-shift to determine urinary levels of 1-hydroxypyrene (Tsai *et al.*, 2002a). Levels of urinary 1-hydroxypyrene increased over time and the highest levels were observed for the post-shift samples on day 5 (Table 1.23). Separate linear regression models were developed for the pelletizers and the packers to determine the association between levels of airborne (gaseous and particle-bound) and dermal PAHs and urinary 1-hydroxypyrene. The study suggests that urinary 1-hydroxypyrene levels on post-shift day 5 could be a suitable indicator for internal doses of PAHs.

Kuhlbusch *et al.* (2004) reported concentrations of organic, elemental and total carbon in bagging facilities at three plants and showed that elemental carbon accounted for 81–92% of total particle mass on the filters.

Table 1.21. Levels of gaseous and particle-bound total PAHs (ng/m^3) from personal measurements in a carbon black manufacturing plant in Taiwan (China)

	No.	Gaseous-phase		Particle-bound	
		Total PAHs	Range	Total PAHs	Range
Pelleting workers	8	1400	556–4120	1200	386–3670
Packers	22	1320	476–4420	1610	471–4810

Adapted from Tsai *et al.* (2002a)
PAH, polycyclic aromatic hydrocarbon

Table 1.22. Levels of gaseous, particle-bound and total PAHs in eight production areas in a carbon black manufacturing plant in Taiwan (China)

	TSM (mg/m^3)	Total (µg/m^3)	Particle-bound (µg/m^3)	Gaseous-phase (µg/m^3)	% Particle-bound
Unloading of feedstock	0.06	7.88	0.02	7.86	0.25
Furnace	0.09	3.22	0.01	3.21	0.3
Filtering/micro-pulverisation	0.07	1.65	0.02	1.63	1.1
Pelletizing	0.23	1.86	0.07	1.79	3.7
Packaging	2.04	1.99	0.61	1.38	30.8
Office/outside	0.12	0.37	0.00	0.37	0
Office/inside	0.08	1.45	0.01	1.44	0.7
Boundary	0.05	0.33	0.00	0.33	0

Adapted from Tsai *et al.* (2002b)
PAH, polycyclic aromatic hydrocarbon; TSM, total suspended matter

Table 1.23. Levels of urinary 1-hydroxypyrene (µg/g creatinine) of pelleting workers and packers at day 1 pre-shift, day 1 post-shift and day 5 post-shift

	Day 1 pre-shift		Day 1 post-shift		Day 5 post-shift	
	AM	Range	AM	Range	AM	Range
Pelleting	1.00	0.85–1.19	1.67	1.00–2.68	4.24	1.01–9.84
Packaging	0.976	0.68–1.19	2.22	0.95–4.20	4.97	2.19–12.7

Adapted from Tsai *et al.* (2002a)
AM, arithmetic mean

(b)   User industries

Information on exposure to carbon black in user industries is not often available; when data are obtainable, they refer to non-specific dust measurements. In the industries, exposure to carbon black is relative to exposure to a complex mixture of particulates. Although results from particulate measurements in these industries may indicate an upper limit of exposure, it was not felt to be informative to review all of the available data on exposures in user industries. This section provides examples of exposure to dust in user industries, but is by no means a comprehensive summary of the available data and must be analysed with caution.

Between July 1972 and January 1977, the Occupational Safety and Health Administration (1977) conducted 85 workplace investigations in the USA to determine compliance with the occupational exposure limit for carbon black of both manufacturers

and users. Approximately 20% of the workplaces inspected were in violation of the exposure limit of 3.5 mg/m^3, and about 60% of these involved exposures that were one to two times higher than the limit.

Several Health Hazard Evaluations have been conducted by the National Institute of Occupational Safety and Health in facilities in the USA that either produced or used carbon black (Belanger & Elesh, 1979; Hollett, 1980; Salisbury, 1980; Boiano & Donohue, 1981). In general, these measurements were below 3.5 mg/m^3, although the studies involved a limited number of samples and a limited number of days over which the measurements were taken.

In the rubber industry, employees are exposed to carbon black mainly in the compounding and Banbury mixing areas. It was reported that the median levels of airborne dust (in which carbon black was one component) in 14 tyre and tube manufacturing plants in the USA were 1.7 mg/m^3 in compounding area samples (individual plant means ranged up to 3.9 mg/m^3) and 1.3 mg/m^3 in the Banbury mixing-area samples (for which the highest plant mean was 4.2 mg/m^3). The values of personal samples were 3.1 mg/m^3 in the compounding area (highest plant mean, 5.0 mg/m^3) and 1.9 mg/m^3 in the Banbury area (highest plant mean, 5.8 mg/m^3) (Williams *et al.*, 1980). A study by the National Institute for Occupational Safety and Health (Heitbrink & McKinnery, 1986) evaluated the effect of control measures at Banbury mixers and the mills beneath the mixers in tyre factories and found lower exposures than those found by Williams *et al.* (1980). The geometric means of exposures of mixer operators at five factories ranged from 0.08 to 1.54 mg/m^3 and those of milling operators at three factories ranged from 0.20 to 1.22 mg/m^3.

Results from studies carried out in the rubber manufacturing industry in Europe in the 1990s are presented in Table 1.24. Two studies were carried out in the Dutch rubber manufacturing industry in the mid- to late 1990s (Meijer *et al.*, 1998; Vermeulen *et al.*, 2000). Vermeulen *et al.* (2000) reported that, since the late 1980s, exposure levels for inhalable particulate in the Dutch rubber manufacturing industry had declined by 5.7% each year. In 1988, the reported mean exposure to inhalable dust (not specifically carbon black) was 5.4 mg/m^3 during compounding/mixing, 2.2 mg/m^3 during pre-treatment and 41.0 mg/m^3 during moulding (Kromhout *et al.*, 1994). The mean exposure in the weighing and mixing areas in five rubber companies in the Netherlands was 2.2 mg/m^3 in 1997 (Vermeulen, personal communication).

Meijer *et al.* (1998) reported dust levels in a manufacturer of rubber conveyor belts. The mean personal level of inhalable dust was 9.4 mg/m^3 during compounding/mixing and 1.1 mg/m^3 during calendering.

Dost *et al.* (2000) published data obtained from occupational hygiene surveys carried out by rubber manufacturers in the United Kingdom. Mean dust exposure in the weighing, mixing and milling parts of the process were 2.3 mg/m^3 in rubber goods manufacture and 2.2 mg/m^3 in rubber tyre manufacture.

Table 1.24. Personal measurements of general dust in rubber manufacturing industry

Country	Industry	Year	Department	N_F	N_S	Dust	GM (mg/m^3)	GSD	Range (mg/m^3)
Netherlands[a]	Rubber conveyor belt	1988–1991	Compounding/ mixing	1	10	Inhalable	8.2	1.9	NS
			Calendering	1	23	Inhalable	0.6	2.6	NS
United Kingdom[b]	Rubber goods	1995–97	Weighing, mixing and milling	NS	82	NS	NS	NS	0.02–18.6
	New tyres		Weighing, mixing and milling	NS	22	NS	NS	NS	0.1–9.6
Netherlands[c]	Rubber goods and tyres	1997	Mixing and weighing	5	61	Inhalable	1.0	2.9	0.2–30.3

[a] From Meijer *et al.* (1998)
[b] From Dost *et al.* (2000)
[c] From Vermeulen (personal communication)
GM, geometric mean; GSD, geometric standard deviation; N_F, number of factories in the survey; NR, not reported; N_S, number of samples

Carbon black is used in the production of toners for photocopying machines, during which charging agents and carbon black are mixed to form a resin. This material is then cooled and granulated to a fine powder. As a result, all carbon black is fixed within the matrix of the plastic polymer. All manufacturers supply toner in sealed plastic cartridges. A brief report from the Health and Safety Executive (undated) described occupational dust exposure in a toner production factory. Personal exposures to inhalable dust ranged from 0.01 to 3.95 mg/m^3 ($n = 60$) expressed as 6–8-hour time-weighted averages (TWA). [Assuming 15% of this dust is carbon black, this gives the range of exposure of 0.001– 0.6 mg/m^3 carbon black.] (Health and Safety Executive, 2004)

In a toner cartridge-recycling site, total dust concentration in various places on the site measured in 1996 ranged from 0.03 to 1.06 mg/m^3 (Health and Safety Executive, 2004).

1.3.3   *Ambient air*

In 1978, it was estimated that 1240 tonnes of carbon black were emitted during carbon black manufacture in the USA (Rawlings & Hughes, 1979). Table 1.25 summarizes typical particulate emissions of carbon black into the air during various stages of its manufacture by the oil-furnace process before 1979. The particulate matter was reported to comprise carbon black (McBath, 1979).

Rivin and Smith (1982) reviewed the literature on emissions of carbon black into the atmosphere during its manufacture. Modern carbon black plants generally employ bag filters to reduce emissions; discharge from a bag filter in good condition during this process (under normal conditions) reportedly contains less than 50 mg/m^3 carbon black (wet basis), a concentration that is not visible (Johnson & Eberline, 1978).

Table 1.25. Typical particulate emissions during the manufacture of carbon black by the oil-furnace process

Source	Range (kg/tonne)	Average (kg/tonne)
Main process vent (uncontrolled)	0.1–5	3.27
Flare	1.2–1.5	1.35
Carbon monoxide boiler and incinerator	–	1.04
Dryer vent		
Uncontrolled	0.05–0.40	0.23
Bag filter	0.01–0.40	0.12
Scrubber	0.01–0.70	0.36
Pneumatic system vent		
Bag filter	0.06–0.70	0.29
Vacuum clean-up system vent		
Bag filter	0.01–0.05	0.03
Fugitive emissions	–	0.10
Solid waste incinerator (where used)	–	0.12

From McBath (1979)

1.4   Regulations and guidelines

Occupational exposure limits and guidelines for carbon black in several countries are presented in Table 1.26.

Table 1.26. Occupational exposure standards and guidelines for carbon black

Country or region	Concentration (mg/m³)	Interpretation	Carcinogenicity
Australia	3	TWA	
Belgium	3.6	TWA	
Brazil	3.5	TWA	
China	4 (T)	TWA	
	8	STEL	
Canada			
British Columbia	3.5	TWA	
	7	STEL	
Quebec	3.5	TWA	
Czech Republic	2	TWA	
Denmark	3.5	TWA	K
Finland	3.5	TWA	
	7	STEL	
France	3.5	TWA	
Germany		MAK	3B
Hong Kong	3.5	TWA	A4
Ireland	3.7	TWA	
	7	STEL	
Italy	3.5	TWA	
Japan	1 (R)	TWA; class 2 dust, containing <10% free silica	2B
	4 (T)	TWA; class 2 dust, containing <10% free silica	
Malaysia	3.5	TWA	
Mexico	3.5	TWA	A4
	7	STEL	
Netherlands	3.5	TWA	
New Zealand	3	TWA	
Norway	3.5	TWA	
Poland	4 (TI)	TWA; value applies to technical soot containing not more than 35 mg benzo[*a*]pyrene per kg of soot	
Republic of Korea	3.5	TWA	
Russia	4.0	TWA	

CARBON BLACK 81

Table 1.26 (contd)

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
South Africa	3.5	TWA	
	7	STEL	
Spain	3.5	TWA	
Sweden	3 (T)	TWA	
United Kingdom	3.5 (I)	TWA	
	7	STEL	
USA			
ACGIH (TLV)	3.5	TWA	A4
NIOSH (REL)	3.5	10-h TWA	
OSHA (PEL)	3.5	TWA	Ca

From Direktoratet for Arbejdstilsynet (2002); International Carbon Black Association (2004); ACGIH® Worldwide (2005); Deutsche Forschungsgemeinschaft (2005); Health and Safety Executive (2005); INRS (2005); Työsuojelusäädöksiä (2005)

A4, not classifiable as a human carcinogen; 2B, possibly carcinogenic to humans; 3B, substances for which in-vitro tests or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories; Ca, carcinogen; I, inhalable dust; K, included in the list of substances considered carcinogenic; MAK, maximum concentration in the workplace; PEL, permissible exposure limit; R, respirable dust; REL, recommended exposure limit; STEL, short-term exposure limit; T, total dust; TI, total inhalable; TLV, threshold limit value; TWA, 8-h time-weighted average (unless otherwise specified)

The National Institute of Occupational Safety and Health (1995) considers 'carbon black' to be a material that consists of more than 80% of elemental carbon, in the form of near-spherical colloidal particles and coalesced particle aggregates of colloidal size, that is obtained by the partial combustion or thermal decomposition of hydrocarbons. In the USA, their recommended exposure limit (10-hour TWA) for carbon black is 3.5 mg/m^3. Since some PAHs may be formed during the manufacture of carbon black and may become adsorbed on it, the recommended exposure limit (10-hour TWA) for carbon black in the presence of PAHs is 0.1 mg PAHs/m^3 measured as the cyclohexane-extractable fraction.

The US Food and Drug Administration (2003) has listed two types of carbon black for use as a food contact colourant for polymers in the USA: (1) carbon black manufactured by the channel process or prepared by the impingement process from stripped natural gas; and (2) high-purity furnace black containing total PAHs that should not exceed 0.5 ppm and benzo[*a*]pyrene that should not exceed 5.0 ppb. The high-purity furnace blacks may be used at levels not to exceed 2.5% by weight of the polymer.

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2. Studies of Cancer in Humans

Industrial exposure to carbon black has occurred in the carbon black production industry and in several user industries, including the rubber, paint and printing industries. The risks for cancer associated with these three exposure circumstances have been evaluated previously (IARC, 1982, 1989, 1996).

The Working Group considered that the epidemiological evidence concerning the risk for cancer in user industries where there has been no attempt to identify which of the workers may have been exposed to carbon black carries little weight in the present evaluation. Consequently, in this monograph, attention was restricted to those studies that explicitly attempted to identify workers who had been exposed to carbon black. Studies based on carbon black production workers and some studies of workers in user industries satisfied this criterion.

From the point of view of exposure patterns, the greatest potential for elucidating the carcinogenicity of carbon black would seem to be in the carbon black production industry. A further advantage of studies among producers is the fact that, in this industry, carbon black was the dominant exposure in the industrial environment, whereas workers in other industries were often exposed to complex mixtures of substances, of which carbon black may in some circumstances have been a relatively minor component.

2.1   Industry-based studies

Table 2.1 summarizes industry-based studies including cohort analyses and nested case–control analyses of workers exposed to carbon black.

2.1.1   *Carbon black production*

The occurrence of cancer among employees at carbon black production facilities in the USA has been followed for different periods since 1935 and was initially described in five reports (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961; Robertson & Ingalls, 1980, 1989; Robertson & Inman, 1996) that were reviewed previously (IARC, 1996). Because of some limitations of these studies and because they have been superseded by newer, more complete studies of carbon black workers in the USA, they are not reviewed again here.

A historical cohort study was carried out among carbon black production workers in the United Kingdom (Hodgson & Jones, 1985), the results of which have been evaluated previously (IARC, 1996). Since that time, a new follow-up has been conducted that supersedes the earlier report (Sorahan *et al*., 2001). The later study collected information on a total of 2086 employees who had worked between 1947 and 1974 in any of five major carbon black production factories in the United Kingdom. The precise inclusion

Table 2.1. Industry-based studies of cancer and exposure to carbon black

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Carbon black production							
Sorahan *et al.* (2001), United Kingdom	Male employees in 5 carbon black production plants; manual workers with ≥12 months service; employed between 1947 and 1974 (*n*=1147); mortality follow-up from 1951 to 1996	Exposure assessment using worker records, experts, measurements and job-exposure matrices	All causes All cancer Oesophagus Stomach Bladder Lung and Bronchus	Employed ≥12 months	372 137 6 8 6 61	1.13 (1.02–1.25) 1.42 (1.19–1.68) 1.62 (0.59–3.52) 1.0 (0.43–1.98) 1.73 (0.64–3.77) 1.73 (1.32–2.22)	Adjusted for age; only last job title was available; smoking histories unknown; reference: external/United Kingdom
				Cumulative exposure (mg/m^3.y)			Reference: low exposure (<20 mg/m^3.y)
			Lung	Medium–low (20–49)	11	0.78 (0.36–1.69)	
				Medium–high (50–99)	17	1.85 (0.93–3.68)	
				High (≥100)	20	1.32 (0.68–2.58)	
				p for trend		0.16	

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Dell *et al.* (2006), USA	Employees of 18 carbon black production facilities in several states; employed >1 year since 1930s; inception cohort (*n*=5011); mortality follow-up from inception to 2003	Worked in industry	All causes All cancers All digestive Oesophagus Urinary organs and bladder Lung Lung	All 10–19 years ≥20 years	1326 330 78 11 8 138 26 25	0.74 (0.70–0.78) 0.83 (0.74–0.92) 0.81 (0.65–1.02) 1.15 (0.64–2.09) 0.93 (0.47–1.87) 0.97 (0.82–1.15) 1.09 (0.74–1.59) 0.67 (0.45–0.99)	Adjusted for age, sex, race; many workers with missing information on sex and race and therefore excluded from the analysis; reference: external/state
Wellmann *et al.* (2006), North-Rhine Westphalia, Germany	Male blue-collar workers in a German carbon black produc-tion plant; employed for ≥1 year between 1960 and 1998 and alive in 1976 (*n*=1535); mortality follow-up in local population registries from 1976 to 1998	Exposure assessment using worker records and experts	All causes Oesophagus Stomach Bladder Lung Lung	All workers *Carbon black index* Medium–low Medium–high High	332 3 5 1 50 14 15 2	1.20 (1.08–1.34) 1.2 (0.25–3.54) 0.76 (0.25–1.77) 0.4 (0.0–2.1) 2.18 (1.61–2.87) 1.53 (0.66–3.65) 1.13 (0.49–2.60) 0.4 (0.09–1.86)	Adjusted for age; reference: external/North-Rhine Westphalia rates Age, tobacco smoking; limited information on smoking for 77% of cohort; reference: low
Büchte *et al.* (2006); Morfeld *et al.* (2006a,b) Germany	Re-analyses of data from Wellmann *et al.* (2006) study	Various variations on original data	Lung	*All workers* Different variables of exposure an linear models Re-estimation of SMR	30–50	No trend 1.2–1.5	Adjusted for age, tobacco smoking; many statistical models; almost all showed no effect of carbon black; re-estimation of SMR after apportioning biases due to reference population, smoking and previous exposure Adjusted for age, tobacco smoking, prior exposures

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Carbon black user industries							
Blum *et al.* (1979), USA	Nested case–control study within a cohort of rubber workers active or retired in 1964; cases were deaths due to stomach cancer, 1964–73; 100 cases and 400 matched controls	Experts assessed exposure of each worker to carbon black and three other substances	Stomach	*Moderate or high exposure* Company A Company B	 21 33	**Odds ratio (90% CI)** 1.49 (0.84–2.66) 1.74 (1.02–2.97)	Adjusted for age, race, sex, duration of employment in company; reference: unexposed to carbon black
Bourguet *et al.* (1987), Ohio, USA	Nested case–control study of workers within rubber industry active in 1964 or earlier; cases ascertained in local hospitals (*n*=65); four controls matched to each case on company, year of employment, year of birth (*n*=254).	Intensity of exposure to carbon black and expert assessment	Skin	Low Medium High	14 14 8	0.7 (NG) 1.2 (NG) 0.7 (NG)	Adjusted for company, year of employment, year of birth, rubber stock, extender and lubricating oils, solvents; reference: unexposed to carbon black

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Blair *et al.* (1990), USA	White male employees at 10 plants with exposure to formaldehyde (*n*=20 714)	Expert assessment of exposure to many chemicals, including carbon black	Lung	Ever ≥20 years	20 6	1.3 [0.8–2.0] 2.4 [0.9–5.2]	Adjusted for age; reference: external/USA
Straif *et al.* (2000), Germany	Blue-collar workers in 5 German rubber companies employed after 1950 and alive in 1981 (*n*=8933); mortality follow-up, 1981–1991	Estimates of exposure to nitrosamines, asbestos, talc and carbon black by intensive exposure assessment using worker records, experts and measurements	Stomach Lung Larynx	*Exposed* >1 year >10 years >1 year >10 years >1 year	12 11 38 24 4	1.8 (0.9–3.4) 1.2 (0.5–3.0) 3.3 (1.6–6.5) 1.5 (0.5–4.6) 1.5 (1.0–2.2) 1.1 (0.7–1.9) 1.5 (0.9–2.4) 1.1 (0.6–2.2) 5.3 (1.3–21.4)	Adjusted for age Adjusted for age, nitrosamines, asbestos, talc Adjusted for age Adjusted for age, nitrosamines, asbestos, talc Adjusted for age Adjusted for age, nitrosamines, asbestos, talc Adjusted for age Adjusted for age, nitrosamines, asbestos, talc Adjusted for age Reference: unexposed to carbon black

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Disease/ cancer site	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment factors/ Comments
Puntoni *et al.* (2004), Genoa, Italy	Dockyard workers who transported bags containing carbon black employed 1933–79 (*n*=2101); cancer incidence ascertained in Genoa cancer registry; followed-up 1986–96	Categorization by task and era		*Exposure*		**SIR (95% CI)**	Adjusted for age; poorly documented exposure; reference: external/City of Genoa incidence rates; overlaps with Puntoni *et al.* (2001).
			All cancers	Ever	208	0.95 (0.83–1.09)	
				High	60	0.94 (0.72–1.22)	
			Oesophagus	Ever	4	1.62 (0.44–4.15)	
				High	0	0 (0–4.24)	
			Stomach	Ever	3	0.29 (0.06–0.85)	
				High	1	0.33 (0.01–1.84)	
			Larynx	Ever	14	1.54 (0.84–2.58)	
				High	4	1.53 (0.42–3.93)	
			Lung	Ever	53	1.08 (0.81–1.41)	
				High	15	1.03 (0.58–1.70)	
			Bladder	Ever	32	1.30 (0.89–1.84)	
				High	14	1.97 (1.08–3.30)	
			Mesothelioma	Ever	7	7.5 (3.02–15.47)	
				High	1	3.87 (0.10–21.54)	
			Melanoma	Ever	8	2.88 (1.25–5.68)	
				High	1	1.5 (0.04–8.40)	

CI, confidence interval; NG, not given; SIR, standardized incidence ratio; SMR, standardized mortality ratio

criteria differed from company to company, depending on the availability of historical company records. For three companies, the cohort included all workers hired between 1947 and 1974, while the two others were unable to include workers who left employment before the late 1960s. The subjects who were identified were traced via national vital statistics registers from 1951 onwards or from the date they entered the cohort. The mortality follow-up ended on 31 December 1996, unless truncated by death or emigration. A total of 27 550 person–years of observation were included in the mortality follow-up. Overall, 26% of the study subjects were known to have died during the period of observation. In the entire cohort, a significant excess of mortality was observed compared with national rates standardized mortality ratio [SMR], 1.14; 95% confidence interval [CI], 1.05–1.24; based on 578 deaths). This excess was especially high (SMR, 1.36; 95% CI, 1.15–1.60; based on 145 deaths) among male manual workers with less than 12 months of employment. An even higher excess risk was observed in the entire cohort for mortality from lung cancer (SMR, 1.61; 95% CI, 1.29–2.00; based on 85 deaths), although, in the case of lung cancer, there was little difference in SMRs between male manual workers with less than 12 months and those with longer employment. The authors contended that there was little evidence of a 'healthy worker effect' bias and also that workers with less than 12 months of employment comprised a subgroup whose mortality experience was unlikely to be linked to employment in carbon black facilities. They therefore focused on a subgroup of 1147 male manual workers with over 12 months of employment in the industry for whom a highly significant SMR for lung cancer of 1.73 (95% CI, 1.32–2.22; based on 61 deaths) was observed. For cancer at most other sites, fewer than five cases were observed. For no other site did the lower bound of the 95% CI exceed 0.75. When using local area rates instead of national rates as a reference, the SMRs for total mortality and for mortality from lung cancer were slightly higher. When SMRs for lung cancer were assessed separately for each factory, two factories had particularly high SMRs, one had a slightly elevated SMR and two had too few subjects to provide informative SMR estimates. Results were ambiguous when SMRs for lung cancer were estimated by time since first employment or by job title. [While no data were available on tobacco smoking habits in this population, the fact that mortality from non-malignant respiratory disease was not elevated provides indirect evidence that, in this study, smoking habits did not differ greatly from those of the general population.]

To understand better the reasons for the excess risk for lung cancer in this cohort, Sorahan *et al*. (2001) carried out an internal study in which an intensive effort was made to estimate the exposure of study subjects to carbon black. Information on work history was collected for each worker, including the dates of starting and cessation of employment and last job title. In some factories, additional information was available. The three smallest factories had closed down by the late 1970s. The two factories that were still operating were visited by the investigators and available information relating to personal and static exposure, rate and capacity of production, purchase records and process equipment was collected for the study period. This information was complemented with data obtained through interviews of long-standing employees, and

detailed histories of the two sites were prepared. Using a combination of sources, including a database of measurements of carbon black taken during the period 1987–95 at 19 European plants among which were two of the factories from this study, and anecdotal reports on the nature of earlier conditions, a job–exposure matrix for exposure to inhalable dust was constructed, demarcated in 5- or 10-year periods. The job–exposure matrix used 12 broad job categories as the job axis. Each of the 120 job titles abstracted from employment records was allocated to one of these 12 broader job categories. Individual work history data were linked to the job–exposure matrix to produce individual estimates of cumulative exposure to carbon black, as a time-dependent variable. For internal analyses, attention was focused on lung cancer and non-malignant diseases of the respiratory system in male manual workers employed for 12 months or more. Poisson regression models included the following variables: attained age, calendar period, year of starting employment, period from first employment, employment status (still employed/left employment), factory and estimated cumulative exposure to carbon black. Variables were treated as categorical. Cumulative exposure to carbon black was categorized in the following groups in units of mg/m^3–year: <20, 20–49, 50–99 and ≥100. The results were expressed as relative risks compared with the lowest exposure group. For all causes of death other than lung cancer, there was no indication that workers with high exposure to carbon black were at excess risk compared with workers with low exposure. For lung cancer, however, the results were more ambiguous. In a statistical model that adjusted only for age, the relative risk in the two highest exposure subgroups was 1.85 (95% CI, 0.93–3.68; based on 17 deaths) and 1.32 (95% CI, 0.68–2.58; based on 20 deaths), respectively, and the *p*-value for trend was 0.16. When a multitude of other covariates was included in the models, the relative risk estimates in these two subgroups dropped to 1.57 (95% CI, 0.74–3.34) and 0.89 (95% CI, 0.40–2.01), respectively. [The Working Group noted that the inclusion of all the covariates, including the factory variable and date of hire, may have constituted overadjustment and regarded the estimates adjusted for age as more informative for the carcinogenicity of carbon black.] When analyses were run that discounted the previous 20 years of exposure, no excess risk for lung cancer due to carbon black was revealed. The authors reported some results by duration of exposure, both among all workers and among the two factories in which an excess risk was found. Among all workers, there was a suggestion of higher risk with increasing duration of employment; in the subgroup of workers in high-risk factories, there was no such suggestion. [The Working Group noted that the interpretation of this study is uncertain. It is possible that a combination of confounding factors—including smoking, previous occupations, social class and regional effects unrelated to tobacco smoking habits—produced the high SMRs, but there is little evidence to support this possibility. It is also possible that internal analyses were compromised by limitations in the estimation of cumulative exposure to carbon black. These include possible errors in dates of employment, lack of information on all jobs held in the factories, lack of documentary information in three of five plants, quite recent measurements and errors in creating a job–exposure matrix from a limited and possibly unrepresentative set of

CARBON BLACK 97

measurements. The combination of these problems could have led to exposure misclassification to such a degree as to attenuate and distort any true dose–response relations.]

Dell *et al*. (2006) undertook an investigation that aimed to include all workers employed in the carbon black industry in the USA. Workers from 20 plants located throughout the USA were enumerated, including many of those who were studied by Robertson and Ingalls (1980, 1989) and Robertson and Inman (1996). The analysis of mortality was restricted to 18 facilities in which it was possible to identify a date of inception from which all newly employed workers could be enumerated. Only 5011 workers who began employment after these dates of inception and who had at least 1 year of service in a job that probably involved exposure to carbon black were included. Mortality was followed up from 1 year after employment to 2003 or until death through social security files and the National Death Index. Gender was unavailable for 17% of the cohort and race was unavailable for 51%. State rates (age-, sex- and race-adjusted) were used to compute expected values, with various ad-hoc adjustments for the missing information on gender and race. Cause of death was unavailable for 76 cases. The SMR for lung cancer, but not for other causes, was adjusted for missing information on cause of death. Compared with the state rates, the mortality rates among the cohort were not elevated for all causes (SMR, 0.74; 95% CI, 0.70–0.78; based on 1326 deaths), for all cancers (SMR, 0.83; 95% CI, 0.74–0.92; based on 330 deaths), for lung cancer (SMR, 0.97; 95% CI, 0.82–1.15; based on 138 deaths) or for oesophageal cancer (SMR, 1.15; 95% CI, 0.64–2.09; based on 11 deaths), nor were there excess risks among workers with more than 10 years of service. The SMRs for lung cancer were well below 1.00 for workers who had 20 years of employment and increased to the null value at about 30 years after first employment. [The Working Group noted that the SMR for lung cancer during the 20 years following first employment in the industry was unusually low.]

Wellmann *et al*. (2006) carried out a study of the mortality of workers in a large and long-standing carbon black manufacturing plant in Germany, where information on work histories and smoking habits of the employees was available. The cohort was enumerated from entry and exit books from the plant and from personnel charts. A total of 2053 blue-collar workers at the carbon black plant who had been employed continuously for at least 1 year between 1 January 1960 and 31 December 1998 were eligible. The vital status of all employees was ascertained from the local population registries of the latest place of residence. The causes of death of the deceased cohort members were determined from death certificates archived in community health departments and from the respective State Institutes of Statistics. Among all 2053 eligible workers, 1535 were men of German nationality and known to be alive on 1 January 1976. The main analyses were restricted to this cohort, for whom vital status and ascertainment of cause of death were virtually complete. Analyses of cause-specific mortality were restricted to the observation period 1976–98, for which retrospective assessment of cause of death in North-Rhine Westphalia was feasible and follow-up was reasonably complete. SMRs were calculated in relation to rates in the (West) German population and in North-Rhine Westphalia. Compared with

the (West) German population, mortality from all causes was elevated (SMR, 1.20; 95% CI, 1.08–1.34; based on 332 deaths). This was accounted for mainly by excesses in heart diseases (SMR, 1.26), chronic obstructive pulmonary disease (SMR, 1.58) and lung cancer (SMR, 2.18; 95% CI, 1.61–2.87; based on 50 deaths). No mortality from cancer at other sites was in excess, although the numbers were small, with less than seven expected cases for each of the other sites. When North-Rhine Westphalia rates were used, the risk for lung cancer was lower but still elevated (SMR, 1.83; 95% CI, 1.36–2.41; based on 50 deaths). When the cohort was further restricted to workers who started working in this company after 1960 (i.e. eliminating the subcohort of survivors who had started earlier), the SMR was even higher (SMR, 2.89; 95% CI, 2.06–3.94; based on 40 deaths). Data on individual cigarette smoking habits were collected from paper charts of the plant occupational health service. Completeness of information on smoking status increased over time and was reasonably complete after the early 1970s. Overall, information on smoking habits was available for 77% of the cohort. For these men, there was at least one document that described smoking habits reported by the physician and sometimes included information on previous smoking habits. Most frequently, a current smoker was asked for current cigarette consumption only, whereas previous smoking habits were most frequently documented for former smokers. Analyses of risk for lung cancer by smoking category indicated that the smoking variables were valid to some degree, but probably entailed some misclassification. The prevalence of smoking in the reference population increased with age, from 51.6% in the group aged 20–29 years to 75.7% in the group aged ≥79 years. The prevalence of smoking of their contemporaries was slightly higher: 55.1% for the youngest age group and between 80.8% and 89.4% in the older age groups.

To elucidate further the possible role of carbon black as a risk factor, Wellmann *et al*. (2006) performed a detailed exposure assessment by examining personnel charts to reconstruct detailed job histories. Cohort members were then categorized according to their employment for at least 1 year in different departments, such as lampblack, gas black or furnace black production. A semiquantitative scoring system to assign exposure to carbon black to job histories, depending on workplace, occupation and calendar time, was developed in collaboration with experts from the plant who were familiar with historical working conditions. The reconstruction of complete job histories including department, work area and job tasks was successful in 73% of male Germans still alive on 1 January 1976. For most other cohort members, information on work area at least was available. Internal comparisons were made using Poisson regression to assess risk for lung cancer as a function of exposure to carbon black, with adjustment for age and tobacco smoking status. Mortality from lung cancer showed no clear relation with increasing categories of average exposure or several indices of exposure to carbon black. For instance, among workers first employed after 1960, the relative risks in four subgroups with increasing average exposure to carbon black, after adjustment for smoking, were 1.00 (based on nine deaths), 1.53 (95% CI, 0.66–3.55; based on 14 deaths), 1.13 (95% CI, 0.49–2.60; based on 15 deaths) and 0.40 (95% CI, 0.09–1.86; based on two deaths).

CARBON BLACK   99

The cohort of German carbon black workers has been the subject of two sets of re-analysis and a nested case–control study. Morfeld *et al.* (2006a) carried out an extensive series of re-analyses of the internal comparisons based on Cox regression models in contrast to the Poisson regression models used by Wellmann *et al.* (2006). They conducted 6080 analyses by crossing, in a factorial fashion, the following design parameters: study population (total cohort, total cohort with information on tobacco smoking, cohort at inception, cohort at inception with information on tobacco smoking); alternative methods for handling missing data in the job–exposure matrix that was used for exposure assessment (four different versions); a variable for exposure to carbon black (cumulative or a three-variable version with duration, average intensity and current exposure); duration of employment in selected departments; lag periods (0, 5, 10, 15 or 20 years); and various covariates (including date of birth, age or date of employment, active smoker, former smoker). The Cox regression model enabled the exposure variable to be taken into account in a time-related fashion. These variables were modelled as continuous linear variables. [If there had been a non-linear dose–response relationship and depending on the nature of the non-linearity, it may have been missed in these analyses.] A large majority of the analyses showed no trend of increasing risk for lung cancer with increasing exposure to carbon black. Indeed, most linear trends were not positive. An anomalous result for tobacco smoking (former smokers seemed to have a lower risk than nonsmokers) was explained by errors in smoking data for several cases. A positive trend was seen with duration of work in one department (lampblack) in the cohort at inception but not among other workers.

To investigate the reasons for a possible excess SMR for lung cancer in the cohort of German carbon black workers, Büchte *et al.* (2006) carried out a nested case–control study based on the cases identified by Wellmann *et al.* (2006). For each of the 50 cases, two controls were selected from the cohort using incidence density sampling and were matched on date of birth. Supplementary information on smoking history and history of employment before joining the carbon black industry was collected for each subject. Two distinct approaches—one based on a job–exposure matrix and one based on expert opinion—were used to infer exposure to asbestos, quartz, PAHs, nickel and chromium(VI) in previous jobs. In addition, information on exposure in the carbon black plant to asbestos and feedstock oil was collected. For exposure to carbon black, four different criteria were used to define the case–control database: all subjects; all subjects with information on smoking; subjects limited to those employed from 1960 onwards; and subjects limited to those employed from 1960 onwards and who had information on smoking. Further analyses were carried out with a lag period that varied from 0 to 20 years in 5-year increments. Indicator variables of whether the subject had participated in or had been a prisoner of war during the Second World War were also included. Mean cumulative exposure to carbon black was lower among cases than among controls. In most statistical analyses, the odds ratios for carbon black and lung cancer were well below 1.0, often significantly so. There was little relationship between other exposures at the carbon black plant (asbestos, feedstock oil) and risk for lung cancer. However, there were

strong relationships between exposures in previous jobs and risk. Using quartz as a marker, since the exposures were highly correlated, the odds ratios for quartz and lung cancer were greater than 5.0 and were highly significant. In many analyses, a significant protective effect of having participated in the Second World War was also observed, which the authors interpreted as evidence of a 'healthy survivor' phenomenon. [The Working Group noted that the lack of a positive association for carbon black is compatible with the results of the internal analysis of Wellmann *et al.* (2006) and that of Morfeld *et al.* (2006a). The Working Group was perplexed by the extraordinarily high odds ratios associated with exposures that were incurred before the workers entered the carbon black industry. The magnitude of these effects is difficult to reconcile with the known effects of such agents. Equally perplexing was the apparent protective effect of having participated in the Second World War.]

Morfeld *et al.* (2006b) addressed the SMR results using the external reference that was reported by Wellmann *et al.* (2006). In particular, they explored whether the reported high SMRs for lung cancer could be due to choice of an inappropriate national reference population or to inadequate control for the confounding effects of tobacco smoking or other occupational exposures outside the plant. The effect of different reference populations was evaluated by using national (West) German rates, rates for the State of North-Rhine Westphalia and rates for the City of Cologne. The authors used information from Büchte *et al.* (2006) and the methods of Axelson and Steenland (1988) to infer to what extent previous exposures may have contributed to the SMR in the cohort, and estimated that the bias to the SMR was at least 25%. The impact of confounding by tobacco smoking on the SMR was estimated by means of plant and regional data and the same methods of Axelson and Steenland (1988), and was found to have created a possible bias of at least 25%. In total, the net effect of these biases plus consideration of possible misclassification of eligibility for three subjects may have led to an approximate halving of the SMR from 2.2–3.0 to around 1.2–1.5. [The Working Group noted that the methods were complex and the results were difficult to interpret. It is not clear whether adjustment for prior exposure is justified given the possible overestimation of the effect of such exposures.]

A general excess risk for cancer was reported in workers in one carbon black production plant in the former USSR (Troitskaia *et al.*, 1980). [The Working Group noted that neither absolute figures nor the method of calculating observed to expected ratios were given.]

2.1.2   *Carbon black user industries*

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum *et al.* (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer (100 in total) from 1964 to 1973 in two rubber companies. Four controls were matched to each case on age, sex and company. [The criteria for selecting controls were not clear.] Using recorded job

history of each worker, the investigators and a group of environmental hygienists assessed potential exposure in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers, which were mainly talc. While not statistically significant, there was a positive association between exposure to carbon black and stomach cancer (Company A: odds ratio, 1.49; 90% CI, 0.84–2.66); based on 21 cases; Company B: odds ratio, 1.74; 90% CI, 1.02–2.97 based on 33 cases). There was some indication that the most highly exposed workers experienced the highest risk.

A nested case–control study was conducted in the tyre and rubber manufacturing industry in the USA to examine the association of squamous-cell carcinoma of the skin with rubber manufacturing materials that were presumed to be contaminated by PAHs (Bourguet *et al*., 1987). Cases of skin cancer were identified from the records of four hospitals located in Akron, OH, and these were cross-checked against a list of past and present employees of two local rubber companies who had been enumerated in 1964 for historical cohort studies conducted previously in this industry. Sixty-five cases of squamous-cell skin cancer in white men were thereby ascertained in this cohort. [The case ascertainment system may not have identified all cases in the cohort.] Controls were selected from remaining cohort members and were matched to cases on company, year of birth and year of employment, and were required to have been employed in the industry until date of diagnosis or date of leaving the industry of the corresponding case. A total of 254 matched controls were identified, with approximately four matched controls selected for each case. Two industrial hygienists assessed the exposure of each study subject to five substances: carbon black, extender oils, lubricating oils, rubber solvents and rubber stocks. Conditional logistic regression analyses were carried out with all five substances included in the models, and each one was categorized into three exposure subgroups reflecting concentration and frequency of exposure. For carbon black, the odds ratios in the low-, medium- and high-exposure subgroups were 0.7, 1.2 and 0.7, respectively, indicating the lack of an exposure–response relationship. There was also no evidence for a trend by duration of exposure.

A historical cohort of 26 561 workers employed in 10 facilities was assembled to evaluate risks for cancer associated with exposure to formaldehyde (Blair *et al*. 1990); 20 714 white men were included in the analysis. The plants were drawn from a variety of industries in which exposure to formaldehyde can be substantial and were located throughout the USA. The project was characterized by a very extensive assessment of exposure to formaldehyde. About 85% of the workers were thought to have been exposed to formaldehyde at levels above 0.1 ppm [0.123 mg/m^3]. To assess possible confounding and modification of effect due to other occupational substances, an assessment was made of the exposure of each worker to several other substances, one of which was carbon black. The exposure status of subjects was inferred from their recorded work histories that were linked to estimates of exposure in different jobs in these plants. The latter estimates were derived by industrial hygienists who carried out site visits, discussed exposure conditions with workers and plant managers and consulted available hygiene monitoring data. Although this study was not designed primarily to assess risk in relation to exposure

102   IARC MONOGRAPHS VOLUME 93

to carbon black, the data could be used for that purpose, and, in one report that focused primarily on exposure to formaldehyde and the risk for lung cancer, results were presented that showed the associations between each of the other substances studied and lung cancer. Expected numbers of deaths were computed using national rates. For all levels and durations of exposure to carbon black combined, there was a slight excess risk for lung cancer (SMR, 1.3 [95% CI, 0.8–2.0]; 20 observed cases). Based on 142 observed cases, the SMR for formaldehyde was 1.4 [95% CI, 1.2–1.6] for ≥20 years after first exposure. There was no clear trend by duration of exposure and the pattern of results was similar when restricted to 20 years or more since first exposure. [The Working Group noted that the description of the methods of exposure assessment and analysis for carbon black was limited. It was not clear whether all workers exposed to carbon black were also exposed to formaldehyde.]

A series of investigations was conducted to assess risks for cancer in the German rubber industry (Weiland *et al*., 1996; Straif *et al*., 1998; Weiland *et al*., 1998; Straif *et al*., 1999). While the initial series of reports addressed risks in the industry as a whole and in selected work areas, one report entailed an attempt to link cancer occurrence to selected occupational exposures, one of which was carbon black (Straif *et al*., 2000). The cohort in which this analysis was conducted comprised 8933 male German rubber workers, and included all male German blue-collar workers in five study plants who were employed during or after 1950 and who were alive and actively employed or retired on 1 January 1981. Follow-up of individual cohort members began on 1 January 1981, but not before completion of 1 year of employment, and ended at the age of 85 years, at death or at the end of the follow-up period (31 December 1991). Cohort members were identified through the computerized files of the health insurance companies and the personnel files of the rubber plants. At the start of follow-up, the cohort of 8933 workers included 6875 actively employed and 2058 retirees. Health insurance data, personnel files and population registries of the participating plants were used to determine the vital status of cohort members at the end of the observation period. Overall ascertainment of vital status for the cohort was nearly complete (99.7%). For all cohort members who were reported to have died, information from the population registry was used to request a copy of the death certificate from the respective community health department. Death certificates were successfully obtained for 2631 (96.8%) of the decedents. In comparison with the general population of western Germany, mortality from all causes was slightly elevated in the cohort of men (SMR, 1.03; 95% CI, 0.98–1.09; based on 1521 deaths). This increased mortality was concentrated among the subcohort of retirees (SMR, 1.13; 95% CI, 1.08–1.18; based on 1992 deaths), whereas the active employees showed a slightly lower SMR of 0.95 (95% CI, 0.89–1.03; based on 727 deaths) for all causes. SMRs for cancers of the stomach, larynx and lung were increased among the total cohort.

To explore further the risks related to specific exposures in this industry, the investigators (Straif *et al*., 2000) estimated the exposure of each cohort member to selected substances, namely nitrosamines, asbestos, talc and carbon black. Individual work histories within the rubber companies were reconstructed using routinely

documented and archived cost centre codes. Complete individual work histories (date of employment, work history within the rubber industry and date of termination) were available for 98.9% of the cohort members from the start of their employment. Since environmental monitoring of the compounds of interest was not performed before 1979, it was necessary to make retrospective semiquantitative estimates of exposure. In cooperation with industrial hygienists from the rubber plants involved and other experts, a scheme for exposure categorization was developed. Exposure to carbon black was rated in a dichotomous fashion (exposed versus unexposed). Complete exposure assessment was available for approximately 95% of the cohort members. Approximately one in every three cohort members was exposed to medium or high levels of asbestos and talc, and almost 20% were exposed to carbon black. In analyses that included one exposure variable at a time, mortality from stomach cancer was increased among workers with exposures to asbestos, talc and carbon black. Depending on the cut-off points used to define low- and high-exposure subgroups, the hazard rate ratio for the effect of carbon black on stomach cancer was between 1.8 (95% CI, 0.9–3.4; based on 12 deaths) and 3.3 (95% CI, 1.6–6.5; based on 11 deaths; >10 years of exposure). However, when asbestos, talc (potentially contaminated with asbestos) and nitrosamines were entered into the model, the hazard rate ratio for carbon black fell to the range of 1.2 (95% CI, 0.5–3.0) to 1.5 (95% CI, 0.5–4.6; >10 years of exposure). [Acknowledgement that the fully adjusted model is more appropriate implies acceptance that talc and/or asbestos are true risk factors for stomach cancer. Until and if such a hypothesis is accepted, the Working Group was inclined to view the significant odds ratios between carbon black and stomach cancer as meaningful.] In parallel analyses of lung cancer, a similar pattern was seen. In analyses in which carbon black was the only exposure variable, the hazard rate ratios were around 1.5 (95% CI, 1.0–2.2; based on 38 deaths) and 1.5 (95% CI, 0.9–2.4; based on 24 deaths; >10 years of exposure), depending on exposure categorization. When the other occupational exposures (nitrosamines, asbestos, talc) were included in the model, the estimates for carbon black dropped to 1.1 (95% CI, 0.7–1.9) and 1.1 (95% CI, 0.6–2.2; >10 years of exposure). [The Working Group considered that it is possible that the carbon black-associated risks for lung cancer may have been confounded by exposure to asbestos.] Analyses of laryngeal cancer were limited by small numbers. In models that used one exposure at a time, carbon black showed a hazard rate ratio of 5.3 (95% CI, 1.3–21.4; based on four deaths). There were also excess risks noted in relation to exposure to talc and asbestos. [While cigarette smoking is a plausible confounder in analyses that use comparisons with external reference populations, this is a much less probable explanation for any associations found in these internal analyses that compared one group of rubber industry workers with another. In addition, the exposure assessment for carbon black was rather crude.]

Puntoni *et al.* (2001, 2004) reported on cancer risks among a cohort of Italian dockyard workers with presumed exposure to carbon black. Between 1947 and 1957, longshoremen in the port of Genoa unloaded between 8000 and 12 000 tonnes of carbon black per year; the bags were often carried on workers' shoulders and thereby produced

considerable exposure to dust. Subsequently, the quantity of carbon black unloaded at the port decreased substantially. The cohort of workers comprised all dock workers employed at three dockyard companies between 1933 and 1979. A total of 2286 male workers were included and were categorized *a priori* into subgroups with varying exposures to carbon black. Longshoremen who unloaded carbon black pallets by forklift trucks and cranes were thought to have low or moderate exposure, depending on the frequency of the task. Men who carried carbon black in paper sacks on their shoulders had high exposure. The vital status of each man was ascertained from the demographic registry of his place of residence until 31 December 1996. Cancer frequency was established by record linkage with the Genoa cancer registry for the period 1986–96 (the interval for which data were available). Individuals who emigrated (n=16) or died (n=169) before 1986, i.e. the starting date of follow-up, were excluded from the analysis. Thus 858, 709 and 534 dockyard workers with low, moderate and high exposure to carbon black, respectively, were eligible for statistical analysis. Expected values were calculated using the population of the City of Genoa. Standardized incidence ratios (SIRs) that used the low-exposure group as reference provided an internal comparison of risk. In the entire study group, 208 cancers occurred during the follow-up period (SIR, 0.95; 95% CI, 0.83–1.09). SIRs were significantly increased for pleural mesotheliomas (SIR, 7.51; 95% CI, 3.02–15.47; based on seven cases) and melanoma (SIR, 2.88; 95% CI, 1.25–5.68; based on eight cases). Less markedly increased SIRs were detected for cancer of the larynx (SIR, 1.54; 95% CI, 0.84–2.58; based on 14 cases) and urinary bladder (SIR, 1.30; 95% CI, 0.89–1.84; based on 32 cases). The incidence of lung cancer was not increased (SIR, 1.08; 95% CI, 0.81–1.41; based on 53 cases). No indication of excess risk for cancer of the stomach (SIR, 0.29; 95% CI, 0.06–0.85; based on three cases), skin cancer other than melanoma (SIR, 0.66; 95% CI, 0.36–1.10; based on 14 cases) or cancer of the kidney (SIR, 0.67; 95% CI, 0.22–1.57; based on five cases) was observed. In the subcohort of highly exposed workers, the only statistically significant excess risk was for cancer of the urinary bladder (SIR, 1.97; 95% CI, 1.08–3.30; based on 14 cases). No cancer at other sites, including pleural mesothelioma and melanoma, showed an increased incidence in this subcohort. [The absence of any measurements in this industry during the time of exposure (1947–57) detracts from the ability to link carbon black to the risk estimates. In addition, the narrow period of cancer observation (1986–96) further detracts since cancer occurrence outside this period was ignored. The excess risks observed for mesothelioma and melanoma can be attributed to exposures other than carbon black.]

2.2   Community-based case–control studies

Table 2.2 summarizes community-based case–control studies that examined risks for cancer in workers exposed to carbon black. Of the four reports described, three are drawn from the same population (Siemiatycki, 1991; Parent *et al*., 1996, 2000).

Steineck *et al*. (1990) examined the relationship between urothelial cancer and various occupational exposures in a population-based case–control study in Sweden. The

Table 2.2. Community-based case–control studies of cancer and exposure to carbon black

Reference, study location	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Cancer site	No. of cases/controls	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders
Steineck et al. (1990), Stockholm, Sweden	Male incident cases during 1985–87; 80% response rate	Population controls; frequency-matched on sex and year of birth	Self-reported job history reviewed by experts	Ever exposed to carbon black	Urothelium	254/287	14	2.0 (0.8–4.9)	Year of birth, smoking
Siemiatycki (1991), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Cancer controls; not matched	Self-reported job history reviewed by experts	Ever exposed to carbon black	Oesophagus Stomach Lung Urinary bladder Kidney Skin melanoma	99/2546 251/2379 857/1360 484/1879 177/2481 103/2525	11 9 52 26 14 2	2.2 (1.2–3.9) 0.8 (0.4–1.3) 1.6 (1.1–2.2) 1.2 (0.8–1.8) 1.9 (1.1–3.0) 0.4 (0.1–1.4)	Age, SES, ethnicity, smoking; 90% CI
Parent et al. (1996), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Cancer controls; population controls, age-stratified	Self-reported job history reviewed by experts	'High' exposure to carbon black	Lung	857/1360 cancer 857/533 pop.	18 18	2.17 (0.95–4.91) 1.52 (0.58–3.97)	Age, ethnicity, SES, proxy/self-respondent, alcohol, asbestos, chromium, tobacco smoking
Parent et al. (2000), Montréal, Canada	Male incident cases from 1979 to 1985; 82% response rate	Population controls plus a random sample of cancer controls	Self-reported job history reviewed by experts	Any 'Substan-tial'	Oesophagus	99/533 pop. 99/533 cancer	11 2	2.1 (1.0–4.3) 5.7 (0.9–36)	Age, ethnicity, education, birthplace, proxy/self-respondent, alcohol, ß-carotene index, smoking

CI, confidence interval; pop., population; SES, socioeconomic status

study was based on men who were born between 1911 and 1945 and who lived in the county of Stockholm for all or part of the observation period of September 1985 to November 1987. Incident cases of urothelial cancer and/or squamous-cell carcinoma in the lower urinary tract were identified from the regional cancer registry and urological departments (*n*=320). Controls (*n*=363) were selected by stratified random sampling (by gender and year of birth) during the observation period from a computerized register that covered the population of Stockholm. Information on exposure was collected by a postal questionnaire and all subjects were contacted at their homes. An industrial hygienist classified the subjects as having been exposed or unexposed to 38 agents and groups of substances, one of which was carbon black. The adjusted odds ratio among men who were classified as having been exposed to carbon black was 2.0 (95% CI, 0.8–4.9; based on 14 cases), but they could also have been exposed to other substances, such as printing inks.

A population-based case–control study of cancer among male residents of Montréal, Canada, aged 35–70 years, included histologically confirmed cases of cancer at 11 major sites that were newly diagnosed between 1979 and 1985 (Siemiatycki, 1991). With a response rate of 82%, 3730 cancer patients were successfully interviewed. For each cancer site analysed, two control groups were used, which gave rise to two separate sets of analyses and results: one control group was selected from among cases of cancer at the other sites studied (cancer controls; see Table 2.2) and another group consisted of 533 age-stratified population controls from the general population (response rate, 72%). The interview was designed to obtain detailed lifetime job histories and information on potential confounders. Each job was reviewed by industrial hygienists who translated jobs into occupational exposures, using a checklist of 293 common occupational substances. Five per cent of the entire study population had been exposed to carbon black at some time (i.e. lifetime exposure prevalence). Among the main occupations in which exposure to carbon black was attributed in this study were painters (26%), printing industry workers (17%), motor vehicle mechanics (8%) and occupations in rubber and plastics products (6%) (Parent *et al*., 1996). The results presented (Siemiatycki, 1991) were based mainly in comparison with the cancer control group. For the following cancer sites, there was no indication of a significant excess risk in relation to any exposure to carbon black, after adjustment for age, ethnic group, social class and tobacco smoking (number of exposed cases; odds ratio): stomach (*n*=9; 0.8), colon (*n*=17; 0.7), rectum (*n*=10; 0.7), pancreas (*n*=3; 0.7), prostate (*n*=25; 1.2), urinary bladder (*n*=26; 1.2), skin melanoma (*n*=2; 0.4) and non-Hodgkin lymphoma (*n*=9; 0.9). For the following sites there was an indication of excess risk: oesophagus (odds ratio, 2.2; 90% CI, 1.2–3.9; 11 exposed cases), kidney (odds ratio, 1.9; 90% CI, 1.1–3.0; 14 exposed cases) and lung (odds ratio, 1.6; 90% CI, 1.1–2.3; 52 exposed cases).

To investigate further the possible link between carbon black and lung cancer, an additional analysis of the Montréal data set was carried out (Parent *et al*., 1996). A synthetic exposure index was created that was composed of the indices deduced for each exposed subject (concentration, frequency, confidence in the attribution of exposure,

duration) and was used to designate a lower and a higher cumulative exposure subgroup. Logistic regression analyses were carried out and were adjusted for the same covariates as those used in the analyses of Siemiatycki (1991), as well as for two recognized lung carcinogens—asbestos and chromium compounds. Using cancer controls, the odds ratios for lower and higher exposure were 1.08 (95% CI, 0.66–1.76) and 2.17 (95% CI, 0.95–4.91), respectively; using population controls, the odds ratios for lower and higher exposure were 0.87 (95% CI, 0.48–1.60) and 1.52 (95% CI, 0.58–3.97), respectively. The excess among highly exposed workers was most pronounced for small-cell tumours of the lung. Based on seven cases, the odds ratio was 5.05 (95% CI, 1.72–14.87) using cancer controls and 4.82 (95% CI, 1.36–17.02) using population controls.

To investigate occupational risk factors for oesophageal cancer in the Montréal study, a separate analysis was conducted that focused on this site only (Parent *et al*., 2000). There were 99 cases of oesophageal cancer, of which 63 were squamous-cell carcinoma. The following variables were entered into the regression models as possible confounders: age (in years), respondent status (self, proxy), education (three levels), birthplace (seven categories), alcohol consumption (three categories), an index of β-carotene intake (three levels) and two tobacco smoking variables (natural logarithm of the number of cigarette–years and smoking patterns: never smokers, former smokers for at least 11 years, former smokers for 3–10 years, former smokers for 2 years or less and current smokers). A separate model was carried out for each of 30 occupational substances, one of which was carbon black. Workers exposed to carbon black at any level had an excess incidence of oesophageal cancer (odds ratio, 2.1; 95% CI, 1.0–4.3; based on 11 cases) and in particular squamous-cell cancer (odds ratio, 3.4; 95% CI, 1.5–7.7; based on 10 cases) when using population-based controls as a comparison group. When other occupational variables were included in a model with carbon black, the results for the latter were not materially affected.

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108   IARC MONOGRAPHS VOLUME 93

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CARBON BLACK   109

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3. Studies of Cancer in Experimental Animals

The studies described below investigated the potential carcinogenicity of carbon black, solvent-extracted carbon black and the materials extracted from carbon black (carbon black extracts). However, individual materials extracted from various carbon blacks are not within the scope of this monograph. Some of these individual components (e.g. nitroaromatic compounds) have been evaluated previously (IARC, 1989, 1996).

Several early studies compared the carcinogenicity of carbon black or carbon black extracts administered orally or by dermal or subcutaneous application. The carbon black used in some of these studies may no longer be commercially available. More recent studies examined the carcinogenicity of inhalation exposure to or intratracheal administration of carbon black or solvent-extracted carbon black. Many of these were part of large studies carried out to investigate the carcinogenicity of diesel exhaust (see also IARC, 1989).

The Working Group identified an issue that relates to the interpretation of several studies on the inhalation and intratracheal instillation of carbon black. A lesion that is frequently seen in treated rats has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell (CKSC) tumour'. Many authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al*., 1993; Carlton, 1994; Dungworth *et al*., 1994; Mauderly *et al*., 1994; Boorman & Seely, 1995; Rittinghausen *et al*., 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain. Therefore, where possible, the Working Group has listed incidences of this lesion separately from those of other pulmonary neoplasms.

3.1 Oral administration

3.1.1 *Mouse*

After two weeks of acclimatization, two groups of 31 and 28 female weanling CF_1 mice were fed 0 (controls) or 2.05 g/kg diet furnace carbon black (ASTM N375) for two years. At necropsy, all tissues were examined for gross pathology. Only tissues that had macroscopically visible lesions were examined histologically. Survival at two years was similar in treated mice (84%) and in controls (71%). No increase in tumour incidence was observed (treated mice: colon tumours, 3%; lung tumours, 23%; controls: colon tumours, 0%; lung tumours, 21%) (Pence & Buddingh, 1985). [The Working Group noted the incomplete histopathological examination.]

3.1.2   *Rat*

After two weeks of acclimatization, two groups of 29 female weanling Sprague-Dawley rats were fed 0 (controls) or 2.05 g/kg diet furnace carbon black (ASTM N375). At necropsy, all tissues were examined for gross pathology. Only tissues that had macroscopically visible lesions were examined histologically. Survival at two years was similar in controls (45%) and treated animals (38%). No increase in tumour incidence was observed (treated rats: colon tumours, 3%; kidney tumours, 3%; mammary tumours, 24%; controls: colon tumours, 3%; kidney tumours, 3%; mammary tumours, 28%) (Pence & Buddingh, 1985). [The Working Group noted the incomplete histopathological examination.]

3.2   Inhalation exposure

3.2.1   *Mouse*

Groups of 80 female Crl: NMRI BR mice, seven weeks of age, were exposed to high-purity furnace carbon black (Printex 90; primary particle size, 14 nm; specific surface area, 227 ± 18.8 m^2/g; MMAD of particles in the exposure chambers, 0.64 μm). The extractable organic mass of the carbon black was 0.04%; the content of benzo[*a*]pyrene was 0.6 pg/mg and that of 1-nitropyrene was <0.5 ng/mg particle mass. The animals were exposed in whole-body exposure chambers for 18 hours per day on 5 days per week to 7.4 mg/m^3 carbon black for 4 months followed by 12.2 mg/m^3 for 9.5 months. After exposure, the mice were kept in clean air for further 9.5 months. A control group was exposed to clean air throughout the study. Histopathology was performed on the nasal and paranasal cavities, larynx, trachea and lung. After 11 months and up to 17 months, body weights were significantly lower (5–7%) in the carbon black-exposed mice compared with controls. During the last months, no difference in body weight was observed between the groups. After 13.5 months, mortality was 20% in the carbon black-exposed mice and 10% in controls; 50% mortality was reached after 19 months in the carbon black-exposed group and after 20 months in the control group. In exposed mice, the lung particle burden was 0.8, 2.3 and 7.4 mg carbon black per lung after 3, 6 and 12 months, respectively; at 12 months, this corresponded to a lung particle burden of 37 mg/g clean-air control lung (wet weight of control lung, 0.2 g). Tumours were only observed in the lung, but no statistical difference was observed between experimental and control animals; 11.3% (9/80) of carbon black-exposed mice had adenomas and 10% (8/80) had adenocarcinomas compared with 25% (20/80) and 15.4% (12/80) of controls, respectively (Heinrich *et al*., 1995).

3.2.2   *Rat*

Two groups of 72 female Wistar rats, seven weeks of age, were exposed by inhalation for 17 hours per day on 5 days per week to 6 mg/m^3 furnace carbon black (Printex 90;

0.04% extractable mass of organics; benzo[*a*]pyrene content, 0.6 pg/mg carbon black; 1-nitropyrene content, <0.5 pg/mg carbon black; primary particle size, 15 nm; MMAD of particles in the exposure chamber, 1.1 μm; specific surface area, 230 m^2/g). One of these groups was exposed for 43 weeks and kept for an additional 86 weeks in clean air and the other group was exposed for 86 weeks and housed in clean air for an additional 43 weeks. Two clean-air control groups of 72 animals were kept for 129 weeks. The respiratory tract of all animals was examined histopathologically. No tumour was observed in the clean-air controls. The 43-week exposure group had a lung tumour rate of 18% [13/72] (two bronchiolar/alveolar adenomas, seven benign CKSC tumours, four bronchiolar/alveolar adenocarcinomas and one squamous-cell carcinoma). The 86-week exposure group had a lung tumour rate of 8% [6/72] (one bronchiolar/alveolar adenoma, four benign CKSC tumours and one squamous-cell carcinoma). In addition to the six tumours, six other rats in the latter group developed lung lesions that were borderline between non-neoplastic and neoplastic (described as marked hyperplasia or marked squamous-cell proliferation). [The difference in the tumour rates of the two exposed groups was not statistically significant] (Dungworth *et al.*, 1994; Heinrich *et al.*, 1994).

A group of 100 female Wistar rats, seven weeks of age, was exposed to high-purity furnace carbon black (Printex 90; particle size 14 nm; specific surface area, 227±18.8 m^2/g; MMAD of particles in the exposure chamber, 0.64 μm). The extractable organic mass of the furnace black was 0.04%; the content of benzo[*a*]pyrene was 0.6 pg/mg and that of 1-nitropyrene was <0.5 ng/mg particle mass. Rats were exposed in whole-body exposure chambers for 18 hours per day on 5 days per week to 7.4 mg/m^3 carbon black for 4 months followed by 12.2 mg/m^3 for 20 months. After exposure, the rats were kept in clean air for further 6 months. Controls (*n*=220) were exposed to clean air throughout the study. Eight groups of 9–21 rats (interim sacrifice groups) were also exposed to carbon black or clean air for 6, 12, 18 or 24 months. Histopathology was performed on the nasal and paranasal cavities, larynx, trachea and lung. Mortality in the carbon black-exposed group was 56% after 24 months of exposure and 92% after 30 months. In the clean air group, mortality was 42% after 24 months and 85% after 30 months. Compared with the controls, the mean lifespan of the treated rats was significantly reduced. Mean body weights were significantly lower from day 300 to the end of exposure (carbon black-exposed, 325 g; control, 417 g). The lung burden of carbon black at 24 months was 43.9±4.3 mg per lung (equivalent to 31.3 mg/g clean-air control lung) and 6.7 mg per animal in the lung-associated lymph nodes (determined after 22 months of exposure). The incidence of benign and malignant lung tumours was increased in the treated groups after 30 months. The numbers of rats with lung tumours are summarized in Table 3.1 (Dungworth *et al.*, 1994; Heinrich *et al.*, 1995).

Three groups of 135–136 female and 138–139 male Fischer 344/N specific pathogen-free rats, 7–9 weeks of age, were exposed in whole-body exposure chambers to 0, 2.5 or 6.5 mg/m^3 furnace carbon black (Elfte × −12) for 16 hours per day on 5 days per week for up to 24 months. The carbon black aerosol was produced by an air-jet dust generator and was diluted with filtered air. The size distribution of carbon black particles in the chamber

Table 3.1. Lung-tumour incidence in female rats exposed to carbon black by inhalation

Exposure period	Carbon black-exposed (average concentration of carbon black, 11.6 mg/m^3)	Clean-air control
Interim sacrifice groups		
6 months	0/20	0/21
12 months	0/18	0/21
18 months	0/16	0/18
24 months	1/9[a]	0/10
Thirty-month study		
	20/100[a]	1/217[b]
	13/100[b]	
	4/100[c]	
	13/100[d]	
No. of animals with tumours[e]	39/100 28/100[f]	1/217

From Heinrich *et al.* (1995)

[a] Benign cystic keratinizing squamous-cell tumours

[b] Adenomas

[c] Squamous-cell carcinomas

[d] Adenocarcinomas

[e] Some animals had two lung tumours

[f] Excluding 11 animals that had only benign cystic keratinizing squamous-cell tumours

was bimodal: 67% of the particles were in the large-size mode (MMAD, 2.0 μm) and 33% in the small-size mode (mass median diffusion diameter, 0.1 μm). The level of extractable organic material was 0.04–0.29% (mean value during the course of exposure, 0.12%). Observations were made throughout lifespan for the majority of rats in each group (i.e. for approximately 100 males and 100 females per experimental group in total) for which body weight, survival and carcinogenicity were evaluated. Three males and three females were killed after 3, 6, 12, 18 or 23 months of exposure. After exposure for 24 months, surviving rats were kept in clean air until mortality reached 90% when the experiment was terminated. The high-dose exposure to carbon black significantly ($P<0.05$) reduced the median lifespan of both females and males. Survival was also significantly reduced in low-dose males. A significant reduction in the body weights of female and male rats exposed to the high dose of carbon black first occurred on days 309 and 449, respectively. This effect was seen only after day 509 of exposure for both males and females in the low-dose group. After about 22 months, the mean reduction in body weight was 16% for high-dose females and 14% for high-dose males; these figures were below 10% in low-dose animals. The exposure caused progressive, dose-related accumulation of carbon black particles in the lungs. After 23 months, the mean lung burden reached 12.4 mg/g in low-dose males, 13.9 mg/g in low-dose females, 20.2 mg/g in high-dose males and 30.0 mg/g in high-dose females. Full necropsies were performed on all animals and lungs and suspected lung tumours were examined microscopically. The incidence of the various types of lung tumour is shown in Table 3.2.

Table 3.2.   Numbers of Fischer 344/N rats with lung neoplasms and numbers and types of lung neoplasm observed after exposure to 2.5 or 6.5 mg/m^3 carbon black for up to 24 months

Type of tumour	Control			Carbon black					
				2.5 mg/m^3			6.5 mg/m^3		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
No. of animals examined[a]	114	118	232	116	115	231	114	115	229
Adenoma									
No. of neoplasms	0	1	1	2	1	3	17	0	17
No. of rats with neoplasms	0	1	1	2	1	3	13	0	13
Adenocarcinoma									
No. of neoplasms	0	1	1	6	1	7	23	1	24
No. of rats with neoplasms	0	1	1	6	1	7	20	1	21
Squamous-cell carcinoma									
No. of neoplasms	0	1	1	0	0	0	1	2	3
No. of rats with neoplasms	0	1	1	0	0	0	1	2	3
Adenosquamous carcinoma									
No. of neoplasms	0	0	0	0	0	0	1	1	2
No. of rats with neoplasms	0	0	0	0	0	0	1	1	2
Malignant tumour not otherwise specified[b]									
No. of neoplasms	0	0	0	1	0	1	0	0	0
No. of rats with neoplasms	0	0	0	1	0	1	0	0	0

From Mauderly *et al.* (1994); Nikula *et al.* (1995)
[a] Including all rats that underwent gross necropsy and microscopic examination of the lung whether the rats died spontaneously, were euthanized or were killed
[b] This tumour was of a mixed mesenchymal and epithelial type

Statistical comparisons were performed using logistic regression modelling. The incidence of adenomas and adenocarcinomas was significantly increased in females, particularly at the high-dose level. There was no significant increase in the incidence of lung tumours in males. The percentages of male and female rats with lung tumours are given in Table 3.3. Exposure-related squamous cysts in the lung were classified as non-neoplastic lesions. In animals that died later than 18 months after the start of the exposure, squamous cysts (one or more per animal) were observed in 0/86 male controls, 1/73 low-dose males and 4/74 high-dose males and in 0/91 control females, 8/90 low-dose females and 13/87 high-dose females (Mauderly *et al*., 1994; Nikula *et al*., 1995).

Table 3.3. Numbers and percentages of Fischer 344/N rats examined for lung neoplasms that had one or more neoplasm following exposure to 2.5 or 6.5 mg/m^3 carbon black for up to 24 months[a]

Group	Sex	No. of rats at risk for neoplasms[b]	Rats with malignant neoplasms		Rats with malignant or benign neoplasms	
			No.	Percentage	No.	Percentage
Control	Female	105	0	0	0	0
	Male	109	2	1.8	3	2.8
	Combined	214	2	0.9	3	1.4
Carbon black						
2.5 mg/m^3	Female	107	7	6.5	8	7.5
	Male	106	1	0.9	2	1.9
	Combined	213	8	3.8	10	4.7
6.5 mg/m^3	Female	105	21	20.0	28	26.7
	Male	106	4	3.8	4	3.8
	Combined	211	25	11.8	32	15.2

From Mauderly *et al*. (1994); Nikula *et al*. (1995)
[a] Each rat with one or more neoplasm was counted only once in each neoplasm category.
[b] Values include all rats examined by gross necropsy and microscopy except those killed at 3, 6 and 12 months. The first lung neoplasm was observed between 12 and 18 months of exposure; thus all rats that died spontaneously or were euthanized in moribund condition plus those killed at 18 months or later were considered to be at risk for lung neoplasms. The total number of rats examined, including those killed at 3, 6 and 12 months, is listed in Table 3.2.

3.2.3   *Hamster*

Thirty-one male golden hamsters [age unspecified] were exposed by inhalation to fine furnace carbon black at various concentrations and for various periods. Six were exposed to 2.98–3.20 mg/ft^3 [~110 mg/m^3] for 53 days, eight to 2.98–3.20 mg/ft^3 [~110 mg/m^3] for 172 days and 17 to 1.55–1.65 mg/ft^3 for 236 days [~57 mg/m^3]. The experiment was terminated from one to 10 days following the end of exposure. No tumours were observed in the larynx or trachea (Snow, 1970).

3.3   Intratracheal administration

Rat

A group of 37 female Wistar rats, 15 weeks of age, was instilled intratracheally with 3 mg/rat furnace carbon black (Printex 90; specific surface area, 270 m^2/g) suspended in 0.9% saline once a week for 15 weeks. A control group of 39 female rats was instilled with 0.4 mL 0.9% saline once a week for 15 weeks. The animals died spontaneously, or were killed when moribund or after 131 weeks. More than 50% of rats in the treated and control groups survived to 100 weeks. The lungs were removed and evaluated microscopically. No primary lung tumour was found in the control group. In the treated animals, 65% [24/37] of the rats had primary lung tumours: three had adenomas, six had adenocarcinomas, one had an adenocarcinoma and a CKSC tumour, four had CKSC tumours, one had a CKSC tumour and an adenoma, three had squamous-cell carcinomas and six rats had squamous-cell carcinomas and additional lung tumours (one adenoma, one adenocarcinoma, three adenocarcinomas and CKSC tumours and one CKSC tumour) (Pott & Roller, 1994; Pott *et al*., 1994).

Groups of 48 female Wistar rats, 7 weeks of age, were treated by intratracheal instillation once a week for 16–17 weeks with approximately 1 mg of one of two types of extracted carbon black (Printex 90 furnace black or Lampblack 101; total particle dose, 15 mg/rat). A control group of 47 rats was treated with the vehicle (0.9% sodium chloride and 0.25% Tween 80 solution). Although the amount of organic material that could be extracted from the two carbon blacks was small (<0.1%), the particles were re-extracted with heated toluene for 4 hours before use. The specific surface areas (extracted) and primary particle sizes of Printex 90 and Lampblack 101 were 270 m^2/g and 14 nm, and 22 m^2/g and 95 nm, respectively. Satellite groups of two to four animals were used to determine the lung particle load 1 day after the last treatment. Both groups showed a lung particle load of 11 mg/lung (8.1 mg/g clean-air control lung). Fifty per cent of the animals in both groups were alive at 18 months. After 27 months, the respiratory tract of all treated animals (that died spontaneously or were killed) was investigated histopathologically. In the Printex 90-treated rats, 10/48 (21%) had lung tumours (*P*<0.001, Fisher's exact test; nine benign CKSC tumours, one bronchiolar/alveolar adenoma and four bronchiolar/alveolar carcinomas). In the Lampblack 101-treated animals, 4/48 rats (8%) had benign CKSC tumours. No lung tumour was observed in the 47 vehicle-treated controls (Heinrich, 1994; Dasenbrock *et al*., 1996). [The Working Group noted that the two types of carbon black investigated induced different tumour incidences, which was due probably to differences in particle size and surface areas.]

Groups of 21–48 female Wistar rats, 8–9 weeks of age, received intratracheal instillations at weekly intervals of one of two carbon blacks—Lampblack 101 (Degussa; mean particle size, 0.095 μm; density, 1.85 g/mL; specific surface area, 18.4 m^2/g) and furnace black (Printex 90; mean particle size, 0.014 μm; [density not specified]; specific surface area, 337 m^2/g) as described in Table 3.4. The dusts had been suspended by ultrasonification in 0.4 mL 0.9% phosphate buffered saline solution and 0.5% Tween 80$^®$

CARBON BLACK 117

Table 3.4. Dose schedules and incidence of lung tumours in female SPF Wistar rats administered carbon black by intratracheal instillation

Dust, size class	Dose instilled	Rats at start/at risk[a]	50% survival (weeks)[b]	Benign lung tumours (%)[c]	Malignant lung tumours (%)[c]	Total lung tumours (%)[c]	Metastases of other tumours to the lung (%)
Lampblack 101	5×6 mg[d]	48/45	106	33.3	26.7	60.0	15.6
	10×6 mg[e]	48/46	104	26.1	37.0	63.0	10.9
	20×6 mg[f]	48/47	108	NH	NH	70.2[g]	NH
Furnace black (Printex 90)	5×1.5 mg[h]	48/46	110	30.4	37.0	67.4	13.0
	5×3 mg[i,j]	21/18	112	22.2	66.7	88.9	11.1
	5×3 mg[j]	27/27	107	22.2	55.5	77.8	22.2
	5×3 mg	48/45		22.2	60.0	82.2	17.8
	5×6 mg	48/48	108	14.6	68.6	83.3	10.4
	10×6 mg	48/47	100	NH	NH	72.3[g]	NH
No treatment	–	48/46	124	2.2	0.0	2.2	4.3

From Pott & Roller (2005)

NH, no histopathology performed

[a] Number of rats examined that survived at least 26 weeks after first instillation

[b] Period after first instillation during which 50% of the animals died excluding rats that died immediately after anaesthesia

[c] Primary lung tumour types diagnosed as benign: adenoma and epithelioma; or malignant: adenocarcinoma and squamous-cell carcinoma; lungs with one or more malignant tumour may also have had benign tumours.

[d–f,h,i] One additional instillation by error. The dust volume of this instillation is included in the calculation of the total volume instilled.

[d] Plus 1×2.5 mg diesel soot

[e] Plus 1×3 mg diesel soot

[f] Plus 1×6 mg diesel soot

[g] Macroscopic examination

[h] Plus 1×3 mg ultrafine hydrophilic titanium dioxide

[i] Plus 1×6 mg ultrafine hydrophilic titanium dioxide

[j] These two subgroups were combined for further statistical calculations. The large difference in tumour response may be due to an inhomogeneous suspension administered to small numbers of rats per subgroup and not caused by the additional instillation of the relatively small volume of titanium dioxide (about 20% of the dose of the first subgroup).

was added to improve the homogeneity of the suspensions. A control group of 48 rats was maintained untreated. Rats were inspected for mortality and clinical signs of morbidity twice per weekday and once a day at weekends. The experiment was terminated after 30 months unless rats were killed when moribund or diagnosed with a growing subcutaneous tumour. After death of the animals and before necropsy of the thoracic and abdominal cavity, lungs were insufflated via the trachea *in situ* with 6% neutral buffered formalin. In particular, the surface of the lung was inspected and lesions were recorded.

The lungs were fixed and embedded in paraffin and sections were strained with haematoxylin–eosin. All tissues suspected of having tumours that were taken from other sites were examined for histopathological lesions, especially for primary tumours that metastasized to the lung. The lung tumour incidence in each group is summarized in Table 3.4. Statistically significant increases in benign and/or malignant lung tumours were observed with both types of carbon black (Pott & Roller, 2005).

3.4   Dermal application

Mouse

Three groups of 12, eight and eight Swiss mice [age and sex not specified] received weekly dermal applications on the clipped dorsal skin of one of three different types of furnace carbon black (Crude 'Kosmos' 40, 33 and 20) suspended in acetone [dose of carbon black not specified] containing 0.5% croton oil. A negative-control group of 20 animals was treated with acetone that contained 0.5% croton oil and a positive-control group of 15 animals was treated with a solution of 1% benzo[*a*]pyrene in acetone that contained 0.5% croton oil. The experiment lasted for 315 days. The site of application was investigated histologically. Two skin papillomas and no carcinomas were detected in the eight 'Kosmos' 33 carbon black-treated animals; no tumours were observed in the two other treated groups or the negative controls. The positive-control group had a tumour incidence of 73%: all tumours were described as squamous-cell carcinomas (von Haam & Mallette, 1952).

In the same study, 14 groups of Swiss mice received weekly dermal applications of 14 different concentrated extracts of carbon black [dose not specified] suspended in acetone that contained 0.5% croton oil. At the end of the experiment at 315 days, six mice with squamous-cell carcinoma with or without additional papillomas were found in four of the 14 groups treated with extracts. Seven mice with papillomas only were found in four other extract-treated groups (von Haam & Mallette, 1952). [The Working Group noted that the types of carbon black used for the extraction and extraction procedure were not given.]

In a series of experiments, a total of 240 CFW white and C3H brown mice [sex unspecified], 6–10 weeks of age, received thrice-weekly dermal applications of three types of carbon black (channel black, thermal black and furnace black) suspended in cottonseed oil, mineral oil or in carboxymethyl cellulose in water on the shaved back for 12–18 months. There was no increased incidence of skin tumours. In the same study, 32 groups of male CFW and C3H mice [number and age of the animals unspecified] received applications of furnace or thermal carbon black extracts (obtained by hot benzene extraction for 48 hours) from eight different carbon blacks for up to 12 months. All but one of the extracts were reported to show moderate to strong carcinogenicity (tumour incidence, 33–85%) [tumour type unspecified]. In an untreated control group of 943 CFW and C3H mice, 13 animals developed malignant neoplasms (six of the skin, six

of the liver and one of the spleen [no further details on the histology]) (Nau *et al.*, 1958). [The Working Group noted several deficiencies in these experiments, namely the use of 1% benzene as a vehicle for some extracts and the limited reporting.]

3.5 Subcutaneous administration

3.5.1 *Mouse*

Ten groups of 50 male and female C57BL mice, 5–5.5 months of age, received subcutaneous administrations of 300 mg furnace carbon black (surface area, 15 m^2/g; average particle diameter, ~80 nm) that contained 0.09 mg benzo[*a*]pyrene and six other PAHs, either suspended in l mL tricaprylin or as a pellet, 300 mg channel carbon black (surface area, 380 m^2/g; average particle diameter, ~17 nm) from which no aromatic hydrocarbons were detected after extraction with benzene ('non-benzo[*a*]pyrene-extractable') either in 1.5 mL tricaprylin or as a pellet, 300 mg channel carbon black plus 0.09 mg benzo[*a*]pyrene either in tricaprylin or as a pellet, the benzene extract from 300 mg furnace carbon black in l mL tricaprylin, the remaining residue from 300 mg furnace carbon black after benzene extraction in l mL tricaprylin, 300 mg furnace carbon black treated for 3 hours with hot chromic acid and suspended in l mL tricaprylin, or 600 mg of an equal mixture of furnace and channel carbon blacks in 1.5 mL tricaprylin. Two further groups of 50 mice received injections of 1 mL tricaprylin (vehicle controls) or 0.09 mg benzo[*a*]pyrene in l mL tricaprylin (positive controls). The experiment was terminated 20 months after injection of the test materials. All suspected tumours found macroscopically were examined microscopically. Tumour incidence was calculated as a percentage and was based on the number of animals alive 5 months after the start of the study, which was the time at which the first deaths from tumours occurred (see Table 3.5). A high incidence of subcutaneous sarcoma (18/46) was observed in mice that received furnace black with extractable benzo[*a*]pyrene administered in tricaprylin, in those that received carbon black extract from furnace carbon black that contained benzo[*a*]pyrene (22/45) and in positive controls (39/41). In the other groups, few or no sarcomas were observed (Steiner, 1954).

In a series of experiments, groups of 10–20 male C3H brown or CFW white mice (total number, 344), 8–10 weeks of age, received a total dose of 17–300 mg of different carbon blacks suspended in cooking oil, tricaprylin or carboxymethyl cellulose in water as one or two subcutaneous injections and were observed for 20 months. The authors reported an 8–13% tumour index in three groups that received subcutaneous injections of carbon black (two furnace blacks and one thermal black) in cooking oil. [The Working Group noted that tumour index was defined by the authors as the percentage of tumours that occurred in animals excluding those found dead of unknown causes and that the tumours were described as 'subcutaneous mixed tumours'.] Groups of 10–30 male C3H and CFW mice, 8–10 weeks of age, also received one or two subcutaneous injections of benzene extracts of several different furnace, channel and thermal carbon blacks in

cooking oil (total dose, 0.01–6.5 mg). In 31/36 groups, tumour (mainly subcutaneous) indices of 15–100% were reported, and 22 of these had an index of >50%. No subcutaneous tumour was observed in the five other groups. Finally, four groups of 19–20 male C3H mice received as one or two subcutaneous injections 0.5–1.0 mL cooking oil that had been incubated with a furnace carbon black for 1–6 months then centrifuged to remove the carbon black; the subcutaneous tumour indices were 17, 67, 81 and 92%. Four control groups of 20–31 C3H mice were injected with 0.5–1.0 mL tricaprylin or cooking oil, and the tumour indices ranged from 0 to 5%. Of a total of 943 untreated CFW and C3H controls, six animals were reported to have malignant skin neoplasms, one [six were reported in Nau *et al*. (1958)] a malignant liver neoplasm and one a malignant spleen neoplasm [no further details on the histology] (Nau *et al*., 1960). [The Working Group noted deficiencies in experimental design and reporting in the above experiments; in particular, difficulty was experienced in interpreting the data that were presented in tabular form.]

Table 3.5. Carcinogenicity of two furnace and channel carbon blacks injected subcutaneously into C57BL mice

Materials tested	Sarcomas/ survivors at 5 months	Tumour incidence (%)	Average of death time (days)
Benzo[a]pyrene-containing furnace black[a], tricaprylin	18/46	39.1	363
Benzo[a]pyrene-containing furnace black[a], pellets	2/47	4.3	411
Non-benzo[a]pyrene-extractable channel black, tricaprylin	0/48	0.0	–
Non-benzo[a]pyrene-extractable channel black, pellets	1/47	2.1	524
Non-benzo[a]pyrene-extractable channel black plus benzo[a]pyrene, tricaprylin	0/43	0.0	–
Non-benzo[a]pyrene-extractable channel black plus benzo[a]pyrene, pellets	0/48	0.0	–
Benzene extract of benzo[a]pyrene-containing furnace black, tricaprylin	22/45	48.9	295
Furnace black[a] residue, tricaprylin	1/37	2.7	405
Benzo[a]pyrene-containing furnace black[a] treated with chromic acid, tricaprylin	0/47	0.0	–
Benzo[a]pyrene-containing furnace black[a] plus non-benzo[a]pyrene-extractable channel black, tricaprylin	0/41	0.0	–
Tricaprylin, 1.0 mL	0/43	0.0	–
Benzo[a]pyrene (0.09 mg), tricaprylin	39/41	95.1	233

From Steiner (1954)
[a] Furnace black from which benzo[a]pyrene and six other PAHs could be extracted with benzene.

3.6   Intraperitoneal administration

Rat

A group of 36 female Wistar rats [age unspecified] received intraperitoneal injections of 20 mg furnace carbon black 'Corax L' suspended in saline once a week for 4 weeks. Fifty per cent of the rats lived longer than 119 weeks and, after 132 weeks, 20% of the animals were still alive. One of 35 animals examined histopathologically at the end of the experiment had a sarcoma in the abdominal cavity (tumours of the uterus were excluded) (Pott *et al*., 1991). [The Working Group noted the low sensitivity of this assay to detect the carcinogenesis of exposure to non-fibrous particles.]

3.7   Combined administration with known carcinogens

3.7.1   *Mouse*

After two weeks of acclimatization, a group of 30 female weanling CF_1 mice was fed 2.05 g/kg diet furnace carbon black (ASTM N375) for 52 weeks and another group of 33 mice received a diet that contained no furnace black. Both groups received six weekly intraperitoneal injections of 20 mg/kg body weight (bw) 1,2-dimethylhydrazine at the start of the study. Survival was similar between treated and control animals. Carbon black did not enhance the incidence of colonic tumours induced by 1,2-dimethylhydrazine (Pence & Buddingh, 1985).

3.7.2   *Rat*

After two weeks of acclimatization, a group of 44 female weanling Sprague-Dawley rats was fed 2.05 g/kg diet furnace carbon black (ASTM N375) for 52 weeks and another group of 45 rats received a diet that contained no furnace black. Both groups received 16 weekly intraperitoneal injections of 10 mg/kg bw 1,2-dimethylhydrazine at the start of the experiment. Survival was similar between treated and control animals. Carbon black did not enhance the incidence of colonic tumours induced by 1,2-dimethylhydrazine (Pence & Buddingh, 1985).

Groups of 72 female Wistar rats, seven weeks of age, were exposed by inhalation to 2.6 mg/m^3 of a PAH-rich hard coal-tar pitch condensation aerosol (T/P aerosol; no carbon particles; benzo[*a*]pyrene content, 50 μg/m^3; MMAD, 0.5 μm) or to mixtures of 2 or 6 mg/m^3 furnace carbon black (Printex 90; see section 3.2.1 for further details) plus 2.6 mg/m^3 T/P aerosol for 17 hours per day on 5 days per week for 43 weeks followed by clean air for 86 weeks or for 86 weeks followed by clean air for 43 weeks. The T/P aerosol condensed onto the surface of the carbon black particles. The experiment was terminated at experimental week 129. When exposed for 43 weeks, lung tumour rates in the groups exposed to both T/P aerosol and carbon black showed an approximately twofold higher increase compared with the group exposed to T/P aerosol only (89/96 and

122   IARC MONOGRAPHS VOLUME 93

72/92 versus 39/97). There was no difference in lung tumour rates between the three
groups exposed for 86 weeks (Heinrich *et al*., 1994).

3.7.3   *Hamster*

Three groups of Syrian golden hamsters [initial numbers, sex and age unspecified]
received 40 weekly intratracheal instillations of carbon black [not further specified] (total
dose, 60 mg/animal) in 0.1 mL saline solution containing 0.5% Tween 80 plus
benzo[*a*]pyrene (total dose, 3, 9 or 9 mg) as a suspension in saline solution. Before
preparing the suspension, benzo[*a*]pyrene was dissolved in acetone and adsorbed on
carbon black to give small benzo[*a*]pyrene crystals. Two other groups of hamsters were
treated with total doses of 3 or 9 mg benzo[*a*]pyrene without carbon black. Between
40 and 43 hamsters per group were examined histopathologically at the end of the
experiment. The incidence of malignant and benign tumours of the larynx, trachea and
lung was reported. The authors stated that carbon black did not enhance the carcinogenic
effect of benzo[*a*]pyrene (Pott & Stöber, 1983). [The Working Group noted the
inadequate reporting of many experimental details in relation to mortality and duration of
the study.]

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CARBON BLACK   123

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124   IARC MONOGRAPHS VOLUME 93

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4. Mechanistic and Other Relevant Data

In this section, the general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discussed. This information is also relevant to the Monographs on titanium dioxide and talc in this Volume.

4.1   Particle deposition, retention and clearance

4.1.1   *Humans*

(a)   *Poorly soluble particles: general introduction*

Few studies are available in humans on the kinetics of clearance and retention of the specific inhaled particles that are discussed in this volume (i.e. carbon black, titanium dioxide and talc). However, for any particles, the probability of their deposition within a given region of the respiratory tract depends on their characteristics and the physical factors that influence their transport in the airstream (e.g. air velocity and airway structure; ICRP, 1994). Deposition by mechanisms of sedimentation and impaction depends on the aerodynamic diameter, while deposition by diffusion depends on the thermodynamic diameter of the particles (ICRP 1994; Environmental Protection Agency, 2004).

Several terms have been adopted in the measurement of aerosols and estimation of the probability of particle deposition in the human respiratory tract (ICRP, 1994; International Standards Organization, 1995; ACGIH®worldwide, 2005). The term 'respirable' refers to particles that can deposit in the alveolar (gas exchange) region of the lungs. Within this monograph, respirable size fractions are defined as ultrafine (< 0.1 μm diameter of primary particle), fine (0.1–2.5 μm) and coarse (> 2.5–10 μm) particles. 'Thoracic' refers to particles that can deposit in the lung airways, while 'inhalable' refers to particles that can deposit anywhere in the respiratory tract. It is recognized that primary ultrafine particles generally exist as aggregates that have a greater surface area than larger primary particles.

A detailed discussion of particle dosimetry in the human respiratory tract can be found elsewhere (Oberdörster, 1988; ICRP, 1994; NCRP, 1997; Environmental Protection Agency, 2004; Bennett & Brown, 2005; Brown *et al*., 2005; Martonen *et al*., 2005). In brief, inhaled particles may be either exhaled or deposited in the extrathoracic, tracheobronchial or pulmonary airways. The deposition of particles in the respiratory tract depends primarily on inhaled particle size, the route of breathing (i.e. through the nose and/or mouth) and the breathing pattern (e.g. volume and frequency). Particles close to 0.3 μm in diameter have minimal mobility, i.e. they are sufficiently large that their diffusive mobility is minimal, yet small enough that their sedimentation and impaction are

IARC MONOGRAPHS VOLUME 93

also minimal. As a consequence, particles in this size range also have minimal deposition in the lung (Fig. 4.1). In general, the deposition fraction of most particle sizes (< 3–4 μm aerodynamic diameter) in humans is greater in the alveolar region than in the tracheobronchial airways. The deposition fraction for particles > 3–4 μm and < 0.01 μm in the alveolar region decreases due to their removal from the extrathoracic (particularly during nasal breathing) and tracheobronchial airways (Fig. 4.1). Of particular relevance to occupational exposures, particles that carry a charge due to the method of their generation (e.g. titanium dioxide) may have increased deposition efficiency in the lungs.

Figure 4.1. Probability of particle deposition in the human respiratory tract by region, according to the ICRP (1994) model. The average deposition has been modelled for an adult breathing through the nose at 25 L/min (light exercise), assuming nasal breathing of spherical particles with a density of 1 g/cm^3
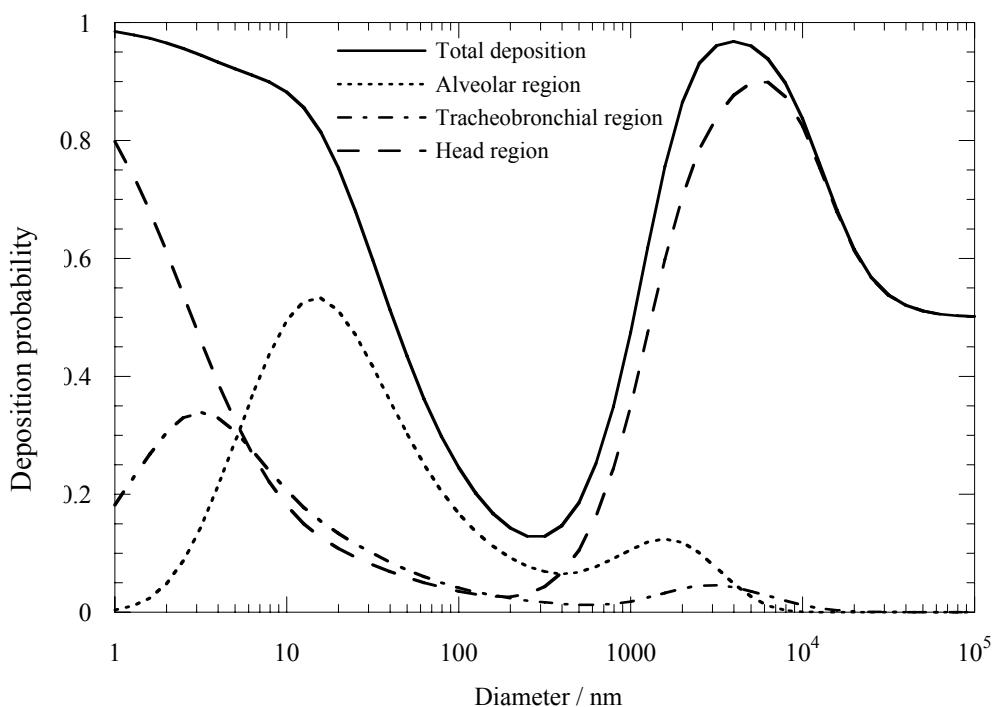
From Maynard & Kuempel (2005)

Particles are frequently aggregates or agglomerates of smaller primary particles. The aerodynamic and thermodynamic properties of these aggregates (rather than the primary particles) affect their behaviour in the air and the probability of their deposition in the respiratory tract. Once deposited, properties such as the size and surface area of both aggregates and primary particles can potentially affect clearance kinetics.

Particle retention in the respiratory tract is determined by the balance between the rate of deposition and the rate of clearance. Particles that deposit in the tracheobronchial region are cleared by mucociliary clearance, which is relatively rapid (retention half-times of approximately 24–48 hours) (IARC, 1996), although some portion of the particles that deposit in the airways is cleared more slowly than expected (Stahlhofen *et al*., 1995). For particles that deposit in the alveolar region, the primary mechanism of clearance is by alveolar macrophage phagocytosis, migration to terminal bronchioles and the 'mucociliary escalator', through which particles are eventually swallowed or expectorated (Oberdörster, 1988). Particles that deposit in the alveolar region are associated with the slow clearance phase (retention half-times of months to years in humans) (Bailey *et al*., 1985; IARC, 1996). In a study of coal miners, little or no clearance of particles was observed (by magnetopneumography) one year after their retirement from the mine (Freedman & Robinson, 1988; Freedman *et al*., 1988). Translocation of particles to the interstitial region increases particle retention time in the lungs (ICRP, 1994). Some fraction of particles that deposit in the alveolar region may also be translocated to the lung-associated lymph nodes. This may occur by transepithelial migration of alveolar macrophages following phagocytosis of the particle or by translocation of free particles to the interstitium, where they may be phagocytosed by interstitial macrophages. Inflammation may alter mucociliary clearance, phagocytosis by alveolar macrophages and the uptake and transport of particles to and through the respiratory epithelium.

Particle deposition and clearance vary among individuals for several reasons, e.g. because of age, gender, smoking status and health status. Pre-existing lung diseases or conditions such as asthma or chronic obstructive pulmonary disease can influence the efficiency and pattern of deposition within the respiratory tract. Deposition also depends on the level of activity and breathing patterns. Deposition and retention determine the initial and retained particle dose to each region and may therefore influence the risk for developing diseases specific to those regions of the respiratory tract.

In summary, the pattern of deposition of particles depends on the particle diameter (aerodynamic or thermodynamic) and on the anatomical and physiological characteristics of the host. The deposition fraction for particles such as carbon black and titanium dioxide within the respiratory tract may vary depending on the size of the agglomerates and influences the dose to a given region of the respiratory tract. Pre-existing lung diseases or conditions can also influence deposition patterns.

(b)   Deposition and retention of inhaled carbon black particles in the human respiratory tract

Several studies describe the deposition and retention of carbon black in the respiratory tract of exposed workers, as well as the health effects of these exposures, which are discussed in Section 4.2.

Although no quantitative data are available, studies of tissues from workers in carbon black factories have shown that widespread deposits of large amounts of carbon black are retained in the lungs (Rosmanith *et al*., 1969; Beck *et al*., 1985).

Lung diseases or conditions (either pre-existing or particle-related) may influence the deposition and retention of particles, e.g. by altering the size, structure and airflow patterns of the airways and by potentially affecting mechanisms of lung clearance. In a recent study of healthy humans who inhaled ultrafine carbon particles (count median diameter (CMD), 0.025 μm; geometric standard deviation (GSD), 1.6), bronchoconstriction may have caused the observed mild dysfunction of the small airways (increased airways resistance, seen as reduced maximal mid-expiratory flow rate [forced expiratory flow ($FEF_{25-75\%}$)]) (Pietropaoli *et al*., 2004). The exposures were relatively low (single 2-hour exposures to 50 μg/m^3, an ambient concentration that is found near major roads) and the individuals were healthy (no pre-existing lung disease). Bronchoconstriction was offered as the most probable mechanism, in part because pulmonary inflammation (as assessed by sputum), which would have been another possible explanation, was not observed. Reduced alveolar gas exchange (measured as reduced carbon monoxide diffusing capacity) was also observed, which was attributed to vasoconstriction. No adverse effects were observed in normal or asthmatic individuals who received single, 2-hour exposures to 10 μg/m^3 ultrafine carbon; the effects observed in the group exposed to 50 μg/m^3 were reversible. Particle deposition was not evaluated in this part of the study. In the same study, the deposition fraction of ultrafine carbon particles was measured in the respiratory tract in healthy and asthmatic subjects at rest and during exercise (Daigle *et al*., 2003; Chalupa *et al*., 2004; Frampton *et al*., 2004). The CMD of the ultrafine carbon aerosol was 0.025 μm (GSD, 1.6) (Pietropaoli *et al*., 2004), and 96% of the particles were elemental carbon (Frampton *et al*., 2004). The deposition fraction of the ultrafine particles in the respiratory tract was measured as the difference in the inspired and expired particle concentrations divided by the inspired concentration (using either mass or number concentration) (Frampton *et al*., 2004). [The Working Group noted that there may be methodological problems in relation to deposition measurements in the above series of studies as commented on by Kim and Jaques (2004).]

Compared with healthy individuals, asthmatics had an approximately 50% higher total deposition fraction of ultrafine carbon particles in the respiratory tract as either total number or mass deposited (Chalupa *et al*., 2004; Frampton *et al*., 2004). In a separate study, Brown *et al*. (2002) reported greater deposition of ultrafine particles in individuals who had obstructive lung disease.

Particle diameter influences deposition, even within the ultrafine particle size range. Daigle *et al*. (2003) and Frampton *et al*. (2004) reported the total ultrafine deposition fraction as particle mass or number, by the midpoint diameter of particle sizes from 7.5 to 75 nm. Within that particle size range, the deposition fraction increased with decreasing particle size, either at rest or with exercise, and among healthy or asthmatic individuals. For example, the deposition fraction for particles with median sizes of 65 nm and 8.7 nm increased from 0.63 to 0.74, respectively, in healthy subjects. During exercise, the deposition fraction increased from 0.84 to 0.94 for the same particle sizes and study group (Frampton *et al*., 2004).

Jaques and Kim (2000) and Kim and Jaques (2004) reported that the total deposition fraction of ultrafine aerosols in humans increased with decreasing particle size (from median diameter of 100 nm to 40 nm). The deposition fraction of particles increased to a similar extent with increases in either tidal volume or respiratory period. During exercise, tidal volume increased and residence time decreased relative to measurements taken at rest. These findings are in contrast to those of Daigle *et al*. (2003). Kim and Jaques (2004) noted that the methodology used by Daigle *et al*. (2003) may cause measurements of exhaled particle concentrations to be variable and erroneous. Furthermore, they asserted that the unusually high deposition values obtained by Daigle *et al*. (2003) were due to an improper sampling of exhaled aerosols. Although the deposition fraction of the particles decreases during exercice on a breath-by-breath basis, the total amount of particle deposition increases with exercise due to an increase in respiratory rate.

Observed and predicted deposition fractions were compared in a study of the total respiratory tract deposition of ultrafine carbon particles. In resting individuals, the observed fractions were found to be similar to those predicted by three deposition models (ICRP, 1994; NCRP, 1997; CIIT & RIVM, 2000 [the 1999 multiple path particle deposition model version from CIIT is cited, but not referenced]; Frampton *et al*., 2004). However, for exercising individuals, the total deposition fractions were higher than those predicted by the models (Frampton *et al*., 2004). This underprediction increased as the particle size increased from 10 to 100 nm; for 26-nm particles, the predicted deposition fraction was 22% lower than that measured in exercising individuals (Frampton *et al*., 2004). Among elderly subjects, the total deposition fraction observed was similar to that predicted from the ICRP (1994) model (although the model slightly overpredicted the deposition fraction of particles smaller than 0.04 or 0.05 μm, and slightly underpredicted the deposition fraction for particles larger than approximately 0.08 μm) (Kim & Jaques, 2005).

Gender was not found to affect the deposition fraction significantly in the Frampton *et al*. (2004) study in the two groups that had sufficient numbers to address this variable. In contrast, Jaques and Kim (2000) reported a greater total deposition fraction in women compared with men with the same breathing pattern, particularly for the smaller ultrafine particles (40 nm), although inter-subject variability was similar.

(c)   Extrapulmonary translocation of carbon particles in humans

The translocation of coal dust particles of respirable size [specific size not noted] from the respiratory tract to other tissue sites has been observed in coal miners. Black pigment observed in the liver and spleen was associated with years in mining and severity of coal workers' pneumoconiosis (LeFevre *et al*., 1982). To reach the liver and spleen, the particles would have had to enter the blood circulation. It is not clear whether this was due to particles being cleared by the mucociliary clearance, being swallowed and entering the gastrointestinal tract and then being taken up in the blood, or whether the particles were able to pass through damaged epithelial and endothelial cells into the blood, as could occur under conditions of disease.

Several studies have been published on the clearance of agglomeration mode carbon particles ([99m]Technetium-labelled carbon particles < 100 nm in diameter [Technegas]; Nemmar *et al*., 2002). The primary particles that compose Technegas are in the range of 5–20 nm (Lemb *et al*., 1993; Lloyd *et al*., 1995). However, before inhalation, these primary particles coagulate into aggregates that have a median diameter in the range of 100 nm to 160 nm (Lemb *et al*., 1993; Lloyd *et al*., 1995; Roth *et al*., 1997). Pulmonary retention of Technegas 45 minute after inhalation was reported by Roth *et al*. (1997) to be 95% and by Isawa *et al*. (1991) to be 98%. According to Brown *et al*. (2002), pulmonary retention 45 minute after inhalation must on average have been less than 67% in the study of Nemmar *et al*. (2002), although these data were not reported. In view of the sharp contrast in the findings of Nemmar *et al*. (2002) and those of others, Brown *et al*. (2002) contended that the results of Nemmar *et al*. (2002) were consistent with the clearance of pertechnetate, but not with that of insoluble ultrafine particles. Mills *et al*. (2006) specifically investigated this supposition. Six hours after inhalation of Technegas, 95.6% of the particles remained in the lungs, and no accumulation of radioactivity was detected in the liver or spleen. In contrast to Nemmar *et al*. (2002), Mills *et al*. (2006) found that ultrafine carbon particles do not pass directly from the lungs into the systemic circulation.

(d)   *Excretion of particle-adsorbed substances*

The retention of particles in the lungs may influence the bioavailability of adsorbed materials. As the retention of particles increases, the potential for adsorbed PAHs to be eluted and absorbed may also increase.

In a study of five nonsmoking warehouse packers in a carbon black (furnace black) manufacturing plant, daily average dust exposures were measured by air sampling, and urinary excretion of 1-hydroxypyrene (derived from pyrene) was measured in post-shift urine samples for five consecutive days during one work week. The mean ambient dust concentrations over the five days ranged from 1.5 to 13 mg/m^3. Excretion of 1-hydroxypyrene ranged from 0.10 to 0.48 μmol/mol creatinine. A regression model showed a statistically significant relationship between weekly mean concentration of airborne dust and 1-hydroxypyrene excretion when the intercept was forced through zero—i.e. assuming zero 1-hydroxypyrene excretion with zero measured dust exposure— but not when the intercept was unconstrained—i.e. allowing for some level of 1-hydroxypyrene at zero measured dust concentration, such as from diet, as noted by the authors, or possibly from previous dust exposures. The urinary excretion was statistically significantly lower on Monday than on other days. The authors concluded that urinary excretion was affected by exposure to dust, and that the pyrene on the dust was bioavailable (Gardiner *et al*., 1992a). [The Working Group noted that the pyrene content of the carbon black was not measured. The airborne sampling method and particle size distribution were not described. Rather than performing the regression analyses based on the mean exposures of individuals for the week, it may be more informative to use the daily values in a mixed model that accounts for correlation within the values of each

individual. Also, the use of a lag could be informative to account for the time between inhalation of dust, metabolism of pyrene and elimination of 1-hydroxypyrene.]

Thirty carbon black workers (eight of whom were involved in wet pelleting and 22 in packaging) were evaluated for their levels of exposure to PAHs. Urine samples were collected on day 1 pre-shift, day 1 post-shift and day 5 post-shift and tested for 1-hydroxypyrene. The inhalable particle-bound PAHs, gaseous PAHs and dermal exposure to PAHs were measured concomitantly. The sampling train contained a filter cassette to collect particles and determine particle-bound PAHs and a sorbent tube to measure gaseous PAHs. Exposure to pyrene was statistically significantly correlated with exposure to PAHs. The results of a multiple linear regression analysis showed no correlations on post-shift day 1, but the values for exposure of the packaging workers to gaseous PAHs and inhalable particle-bound PAHs and dermal exposure to particle-bound PAHs were significantly correlated on post-shift day 5 (Tsai *et al*., 2002).

4.1.2   *Experimental systems*

(a)   Rodent respiratory tract

As in humans and other species, the deposition of particles in the rodent respiratory tract depends on particle characteristics, airflow properties and airway structure. Rats are the most frequently used animals in experimental studies of inhaled particles, and some aspects of the rat respiratory tract that influence the kinetics of particle deposition therein include breathing pattern (nose or mouth), level of activity (resting or exercise) and lung structure (head airways and tracheobronchial branching pattern) (Miller, 2000). Rats are obligatory nose breathers, while humans breathe both through the nose and the mouth, the extent of which varies among individuals and also depends on level of activity (with exertion, the proportion of breathing through the mouth generally increases). Rats have more extensive airways in the nasal region; therefore, particle deposition in this region is greater in rats than in humans. The size of particles that are inhalable (capable of entering respiratory tract) differs between rats and humans (Ménache *et al*., 1995). The airway branching system is symmetric (bi- or tripodal) in humans and asymmetric (monopodal) in rats, which influences the site of deposition (airway impaction tends to be greater in the human tracheobronchial region), and, unlike humans, rats do not have respiratory bronchioles. These factors influence the kinetics of particle deposition in the respiratory tract (Ménache *et al*., 1996).

Once particles are deposited, their removal or retention are based on mechanisms of biological clearance. As for humans, particles in the tracheobronchial region of rats are cleared by the mucociliary pathway and by macrophages in the alveolar region. Particles that enter the interstitium may also enter the lymph and blood circulation. Differences in these physical and physiological factors can result in differences in the clearance rates among species. While tracheobronchial clearance is relatively rapid in both rats and humans (half-times of the order of hours to days), the normal alveolar clearance rate in rats is approximately 10 times faster than that in humans (Snipes, 1989).

Studies in rodents (primarily rats and mice) have shown that the long-term retention of particles is greater than would be predicted from rodent studies that used lower concentrations or durations of exposure. This increase in particle retention has been attributed to the excessive particle loading in alveolar macrophages and impairment of the clearance they mediate (Morrow, 1988; ILSI Risk Science Institute Workshop Participants, 2000). At sufficiently high doses, impaired clearance persists, especially in rat lungs (Bermudez *et al*., 2002, 2004; Elder *et al*., 2005). Muhle *et al*. (1990a) reported impaired alveolar clearance in rats that began at a retained particle mass dose of ~0.5 mg/rat lung and had essentially ceased at ~10 mg/rat lung (fine particles of unit density). In overloaded lungs, particles can translocate more readily to the lung interstitial and lymph nodes, and the fraction that migrates to the lymph nodes increases as the particle size decreases (Bellmann *et al*., 1989).

Lung responses to overloading in rats include increased lung weight, chronic inflammation, fibrosis and lung tumours (Muhle *et al*., 1991). Overloading was originally defined in terms of particle mass or volume dose (Morrow, 1988). However, Morrow (1992) noted that volumetric overloading did not explain the greater retention of ultrafine particles than that expected for a given mass or volume particle dose. Tran *et al*. (1999, 2000) developed a biomathematical exposure–dose–response model in which overloading in rats was based on particle surface area dose and provided a better fit to the experimental data evaluated. Ultrafine carbon black particles may be retained in the lungs to a greater extent than larger respirable particles because they escape alveolar macrophage phagocytosis (Renwick *et al*., 2001, 2004) and enter the lung interstitium (Ferin *et al*., 1992, 1994).

Overloading, as originally defined, refers only to poorly soluble, fine-sized particles of low toxicity. Other factors can also cause impaired clearance, increased particle retention and lung responses similar to those observed in overloading. These factors include cytotoxicity, such as generation of reactive oxygen species on the particle surface (e.g. crystalline silica) (Vallyathan *et al*., 1988), or escape from uptake by alveolar macrophages and entrance into the lung interstitium, as observed for ultrafine particles (Ferin *et al*., 1992, 1994; Renwick *et al*., 2001, 2004). Cytotoxic and ultrafine particles result in impaired clearance at mass doses that are much lower than those associated with classical overload (Muhle *et al*., 1990a; Bellmann *et al*., 1991; Morrow, 1992).

Several reviews, most of which focus on particle toxicity and carcinogenicity, have also described the retention kinetics of particles (including carbon black) after their deposition in the lungs of experimental animals (Morrow, 1988; Snipes, 1989; Kreyling, 1990; Morrow, 1992; Muhle *et al*., 1994; Oberdörster, 1995).

Several studies that are summarized in Table 4.1 evaluated the clearance and retention of different carbon black materials after deposition into the lung following intratracheal instillation into and inhalation by mice and rats. Bowden and Adamson (1984) instilled a

Table 4.1. Kinetics of carbon black (CB) in experimental animals

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Colloidal carbon	30 nm	Swiss mouse	Intratracheal instillation; 4 mg	6 months	Most CB cleared via MC escalator; some transepithelial passage, very low lymphatic clearance; heavily laden AM remained for months in lung	No quantitative results; findings based on qualitative histological data	Bowden & Adamson (1984)
[7]Be-labelled carbon particles (Elftex 8; furnace black)	0.01–1 μm (primary 27 nm)	Swiss mouse (4 weeks and 18 months; female)	Gavage; 7 mg	14 days	[7]Be activity was mainly confined to the gastrointestinal tract; retained dose at 14 days: young, 3.3×10^{-5}%; old, 8.4×10^{-5}%; some activity in non-intestinal tissue	Very small fraction of CB may penetrate via Peyer's patches.	LeFevre & Joel (1986)
RCF-7 (furnace black)	0.22 μm MMAD (primary 37 nm)	Fischer 344 rat	Inhalation, 20 h/day, 7 days/ week; 6.6 mg/m^3	1–11 weeks followed by ^{14}C-diesel exposure for 45 min + 1 year of observation	Linear increase in CB lung burden with duration of exposure; lung burden ~30 mg; increased CB and ^{14}C-diesel pulmonary half-life with increasing lung burden	Retention $t_{1/2}$ was estimated from a two-phase lung retention model with a sequestration term.	Lee *et al*. (1987)
Elftex 12 (furnace black)	0.24 μm MMAD	Fischer 344 rat	Inhalation, 20 h/day, 7 days/ week; 7 mg/m^3	1, 3, 6 weeks exposure, followed by up to 1 year of observation	Lung burdens: 1.1, 3.5, 5.9 mg CB; 1-year retention: 8, 46, 61%; LN burden: 1, 21, 27% of initial CB lung burden; doubling of normal half-life of ~50 days occurred at CB lung burden of ~0.8 mg.	Authors propose AM sequestration model to explain retarded CB clearance at higher CB burden.	Strom *et al*. (1989)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Printex 90 (furnace black)	0.64 μm MMAD (primary 14 nm)	Wistar rat	Inhalation 95 h/week; 7.4 mg/m^3	4.5 months	Retained CB: 13.7 mg; t$_½$ of ^{85}Sr-labelled test particles: 472 days; prolonged half-life of various dusts detectable at rat lung burden of ~0.5 mg; complete impairment of clearance at ~10 mg	Quantitative relationship observed is similar to that of other low-toxicity low-solubility particles.	Creutzenberg et al. (1990); Muhle et al. (1990a)
Printex 90 (furnace black)	0.64 μm MMAD	Wistar rat (female)	Inhalation 19 h/day, 5 days/week; 12 mg/m^3	24 months for CB; 3, 12, 18 months for ^{59}Fe$_2$O$_3$ and ^{85}Sr-poly-styrene particles	CB lung burden: 50.2 mg; CB half-life, 550 days; ^{59}Fe$_2$O$_3$ half-life, 244–591 days; ^{85}Sr half-life, 472 days at 3 months then back to normal half-life of 50–60 days	No data provided to demonstrate lower alveolar deposition of ^{85}Sr particles at high lung burdens.	Creutzenberg et al. (1990); Muhle et al. (1990b, 1994)
Elftex 12 (furnace black)	2–2.4 μm MMAD (large mode) 0.02–0.1 μm DED (small mode, mass, 10–30%)	Fischer 344 rat	Inhalation; 3.5 mg/m^3, 13 mg/m^3 98 mg/m^3	16 h/day, 7 days/week; 6 h/day, 5 days/week; 4 h/day, 1 day/week; 12 weeks exposure + 24 weeks post-exposure	Pulmonary retention half-life similar for different exposure rates; average half-life ~520 days (95% CI, 350–950)		Henderson et al. (1992)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Elftex 12 (furnace black)	2 μm MMAD (large mode) 0.1 μm MMDD (small mode, 33%) 43 m^2/g	Fischer 344/N rat	2.5 mg/m^3, 6.5 mg/m^3	16 h/day, 5 days/week, 24 months	Double exponential clearance; slow phase, no clearance in CB-exposed group compared with half-life in controls of 113–135 days		Mauderly (1994)
Printex 90 (furnace black)	0.64 μm MMAD 227 m^2/g	Wistar rat, NMRI mouse	11.6 mg/m^3 (average)	18 h/day, 5 days/week, 24 months (rat) + 6 months post-exposure or 13.5 months (mouse) + 9.5 months post-exposure	CB accumulation kinetics test particle clearance; CB accumulation in rat and mouse lung similar (at 1 year of exposure)		Heinrich *et al.* (1995)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Carbon	40 nm	Swiss mouse (male, 25 g)	Intratracheal instillation; 2 mg (following bleomycin) Controls: carbon only; bleomycin only	Bleomycin (0.15 units) to induce lung injury, followed by carbon either 3 days or 4 weeks later. Killed 16 weeks after carbon exposure.	Carbon-only: most particles phagocytosed; some particles seen in interstitium and IM; increasing particles in LN by 16 weeks; carbon 3 days after bleomycin: large amount of carbon in fibrotic regions at 16 weeks; significantly higher insoluble residue; carbon 4 weeks after bleomycin: particle deposition in less damaged regions; particle retention similar to carbon only	Some quantitative results of carbon retention, as the retained insoluble residue at 16 weeks; detailed histology in Adamson & Hedgecock (1995); quantitative results of inflammatory cells in BAL, cell proliferation and fibrosis in Adamson & Prieditis (1995).	Adamson & Hedgecock (1995); Adamson & Prieditis (1995)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
9000-type xerographic toner: 90% styrene/n-buthyl-metha-crylate, 10% furnace-type carbon black	MMAD 4.0 µm, GSD 1.5	SPF Fischer 344 rat (6 weeks; female)	Inhalation; 0, 10 and 40 mg/m^3 (respirable concentrations: ~3 and 14 mg/m^3)	6 h/day, 5 days/week, for 3 months; histology at 3 months (end of exposure) and at 18 months; retention half-life measured using: $^{59}Fe_2O_3$, ^{51}Cr-polystyrene, ^{85}Sr-polystyrene (MMAD of 0.3, 0.7, 3.5 µm, respectively).	At 10 mg/m^3: 0.4 mg lung burden; retention half-life: 277 days; slight retardation of alveolar clearance with partial recovery 6 months after end of exposure; At 40 mg/m^3: 3.0 mg lung burden; retention half-life: 2845 days; clearance retardation without reversal; AM (in BAL) without particles increased from 25% at the end of exposure to 85% after 15 months of observation, but AM did not remove the inhaled tracer particles; more migration to LN of smaller tracer particles	Low percentage of carbon black in toner but kinetics may be relevant to carbon black (thermal black) with similar particle size	Bellmann *et al.* (1989, 1992)

Table 4.1 (contd)

Particle type	Particle diameter and surface area	Species (age and sex)	Route of exposure and dose/exposure concentration	Duration of study	Findings	Comments	Reference
Carbon black (Printex-90 and Sterling V)	Printex-90 (HSCb): 14 nm primary particle; MMAD 1.2–2.4 µm (GSD 2.0–3.1); 300 m^2/g. Sterling V (LSCb): 70 nm primary particle; MMAD 0.6–0.9 µm (GSD 3.0–3.7); 37 m^2/g	Fischer 344 rats, B6C3F$_1$ mice and 276 F1B Syrian golden hamsters (5 weeks; female)	Inhalation; Printex-90: 0, 1, 7, 50 mg/m^3 (rats, mice, hamsters); Sterling V: 50 mg/m^3 (rats only).	6 h/day, 5 days/week, for 13 weeks; particle retention and effects measured at end of exposure and at 3 and 11 months post-exposure; retention also measured after 5 weeks of exposure	Similar surface area doses in rat lungs at 7 mg/m^3 HSCb, 50 mg/m^3 LSCb: ~0.3 m^2; similar mass doses at 50 mg/m^3 HSCb or LSCb: ~5.5 mg or ~8 mg, respectively; rats: prolonged particle retention in lungs at 7, 50 mg/m^3 HSCb and at 50 mg/m^3 LSCb (but post-exposure clearance was in LSCb but not at 50 mg/m^3 HSCb); mice: prolonged particle retention in lungs at 7, 50 mg/m^3 (HSCb); hamsters: prolonged retention at 50 mg/m^3 only (HSCb)	PAH content: 0.039 mg/kg (Printex-90); 8.8 mg/kg (Sterling V) (Borm *et al.* 2005)	Elder *et al.* (2005)

AM, alveolar macrophages; BAL, broncheoalveolar lavage fluid; DED, diffusion equivalent diameter; GSD, geometric standard deviation; HSCb, high surface-area carbon black; IM, interstitial macrophages; LN, lymph node; LSCb, low surface-area carbon black; MC, mucociliary; MMAD, mass median aerodynamic diameter; PAH, polycyclic aromatic hydrocarbon

CARBON BLACK 139

very large dose (4 mg, i.e. 4% of the weight of a mouse lung) of colloidal carbon (primary particle size, 30 nm diameter) into the trachea of 60 Swiss Webster mice and followed its clearance in groups of three mice killed at intervals over a 6-month period. Most of the carbon black was cleared via the mucociliary escalator, but some transepithelial passage via type I cells also occurred. Heavily laden alveolar macrophages stayed in the lungs for the whole observation period, and there was some, although low, clearance via the lymphatic system. No quantitative results were reported.

Lee *et al*. (1987) exposed male Fischer 344 rats by inhalation to 6 mg/m^3 carbon black with a MMAD of 0.22 μm in whole-body exposure chambers for 20 hours per day on 7 days per week for 1–11 weeks (for details, see Table 4.1). Immediately following exposure to carbon black, rats were exposed by nose-only inhalation to ^{14}C-labelled diesel exhaust particulates for 45 minute and were followed for 1 year. Inhibition of lung clearance was inferred by the increased retention of radioactive diesel particles as a percentage of initial lung deposition. The percentage of retained particles increased with increasing exposures. The long-term retention half-times (estimated with a two-phase lung retention model with a sequestration term) were 57, 96 and 140 days for the 1-, 3- and 5-week exposure groups, respectively. The results at 11 weeks were not reported. The pulmonary retention of carbon black was similar to that reported for diesel exhaust by Strom *et al*. (1989).

Strom *et al*. (1989) measured the retention of carbon black (furnace black) in rat lungs and thoracic lymph nodes. Male Fischer 344 rats were exposed by inhalation (whole-body) to 7 mg/m^3 carbon black for 20 hours per day on 7 days per week for 1, 3 or 6 weeks and were followed for 1 year. Particle size was 0.07 μm CMD with a MMAD of 0.24 μm. Lung burdens of 1.1, 3.5 and 5.9 mg carbon black were achieved after 1, 3 and 6 weeks of exposure, respectively; the 1-year retention fractions were 8, 46 and 61% of the lung burden at the end of the exposure periods, respectively. At the higher doses, clearance was reduced, and the main transport of particles from the lungs was to the lung-associated lymph nodes. The proportion of carbon black transported to the thoracic lymph nodes increased with increasing exposure—1, 21 and 27% of the initial lung burden at 1, 3 and 6 weeks of exposure, respectively. The authors concluded that a carbon black lung (macrophage compartment) burden in the rat of ~0.8 mg results in a doubling of the normal retention half-time of about 50 days.

Impaired alveolar clearance and increased particle retention were also observed in an inhalation study with several particle types, including carbon black, in Wistar rats (Creutzenberg *et al*., 1990; Muhle *et al*., 1990b). The carbon black (furnace black) was Printex 90, with a primary particle size of approximately 0.014 μm and an MMAD of 0.64 μm. Female Wistar rats were exposed by inhalation (in whole-body chambers) to 7.4 ± 1.5 mg/m^3 for 19 hours per day on 5 days per week for 4.5 months. The carbon black retained in the lungs at the end of 4.5 months of exposure was 13.7 ± 2.0 mg. The retention half-time of subsequently inhaled ^{85}Sr-labelled polystyrene test particles was 472 days in these rats compared with 61 days in air controls. After the 4.5-month exposure to 7.4 mg/m^3, rats were subsequently exposed to 12 mg/m^3 for 19 hours per day

on 5 days per week for up to 24 months (Creutzenberg *et al*., 1990; Muhle *et al*., 1990a,b, 1994). Some groups were exposed for 18 months and then removed from exposure for 6 months. At 3, 6, 12, 18, 22 and 24 months of exposure, the lung and lung-associated lymph node burdens were measured. The highest carbon black lung burden was 50.2 ± 10.9 mg at 18 months, and the lymph node burden was 6.7 mg at 22 months. Interstitial fibrosis was observed in these rats at 12 and 18 months. The pulmonary retention half-times of radiolabelled tracer particles were determined at 3, 12 and 18 months of exposure, and at 18 months followed by 6 months of clean air. The retention half-time for carbon black was 550 days (95% CI, 322–1868 days) following termination of exposure. Test particle clearance of $^{59}Fe_2O_3$ (0.35 μm in diameter) was significantly prolonged with increasing duration of exposure to carbon black, with a half-time that ranged from 244 to 591 days compared with 61–96 days in air controls. In contrast, clearance of ^{85}Sr-labelled polystyrene microsphere (3.5 μm diameter) showed only prolonged retention after 3 months of exposure to carbon black with a half-time of 472 days whereas, at the 12- and 18-month exposure time-points, test particle clearance returned to control values of about 50–60 days. The authors suggested that this was due to a change in the deposition site of the larger ^{85}Sr-labelled polystyrene microspheres as a result of altered lung architecture (in response to carbon black-induced inflammation and other changes) and breathing pattern, and concluded that the retardation of clearance was detectable in rats when the retained lung burden of various dusts exceeded 0.5 mg, and that a substantial decrease in the clearance rate was observed at lung burdens exceeding 10 mg (Creutzenberg *et al*., 1990; Muhle *et al*., 1990b).

Henderson *et al*. (1992) evaluated the pulmonary retention in Fischer 344 rats of furnace black (Elftex 12) inhaled at three different dose rates such that the product of concentration × time was very similar (392 mg × h/m^3 per week). Lung burdens were 3–4 mg. The retention half-time determined over a 24-week period after exposure was not statistically significantly different among the different groups (~520 days; 95% CI, 350–950 days).

Mauderly (1994) studied the retention of tracer doses of [^{7}Be]furnace black (Elftex 12) in Fischer 344/N rats 3 and 18 months after chronic exposure to two concentrations of unlabelled carbon black (2.5 mg/m^3 and 6.5 mg/m^3). Clearance of the labelled carbon black followed a two-exponential model. The most striking difference was found in the slow-phase clearance component, which showed little or no clearance over a period of 126 days for the low- and high-dose groups compared with retention half-times of 113 and 135 days for control rats.

In a study of chronic inhalation in Wistar rats and NMRI mice exposed to furnace black (Printex 90; 11.6 mg/m^3), pulmonary particulate accumulation was measured (Heinrich *et al*., 1995). The rats were exposed for 18 hours per day on 5 days per week for 24 months; the mice were similarly exposed for 13.5 months. Both rats and mice showed similar accumulation kinetics over the exposure time; at 1 year of exposure, the normalized lung burden (mg/g of control lung) was 32 mg in rats and 37 mg in mice. In addition, rats showed significantly prolonged retention of tracer particles compared with

controls as early as 3 months after exposure, which persisted through 12 and 18 months of exposure and 3 months after the 18-month exposure (see Creutzenberg *et al*., 1990).

(b) Retention of intratracheally instilled ultrafine carbon black particles in healthy and injured lungs of mice

Using a rodent model of lung susceptibility, Adamson and Hedgecock (1995) and Adamson and Prieditis (1995) examined the particle distribution and retention of carbon black in healthy or injured (bleomycin-treated) lungs. Following treatment with bleomycin (0.15 units, by intratracheal instillation), male Swiss mice received 2 mg 40-nm carbon black in hydrolysed gel (also by intratracheal instillation) either three days or four weeks later. Groups of four mice were killed at various times up to 16 weeks after administration of the carbon black. Additional groups received carbon black only or bleomycin only. In the carbon black-only group, histological examination a few days after instillation showed that most of the carbon black was inside alveolar macrophages and polymorphonuclear leukocytes, although some particles were seen in the interstitium and interstitial macrophages (remaining for 16 weeks, when most of the alveoli were clear of inflammatory cells and particles); particles were also found in the hilar lymph nodes at 1 week, the amount of which increased by 16 weeks. In contrast, in the mice receiving carbon black 3 days after bleomycin, particles were seen to cross the denuded epithelial surface and, by 4 weeks, 'many carbon black-laden cells' were seen in the connective tissue; by 16 weeks, 'a large amount of carbon black' had been incorporated into the interstitium. In mice treated with carbon black four weeks after treatment with bleomycin, particles were again seen mostly in the air spaces (free or phagocytosed); although the alveolar surface was not denuded, cell composition was abnormal (cuboidal epithelium in fibrotic areas). The amount of carbon black retained in the lungs was assessed at 16 weeks (by digestion of the lungs in 40% potassium hydroxide). The weight of the insoluble residue at 16 weeks was statistically significantly greater (1.6 mg) in mice that received carbon black 3 days after bleomycin (when lung injury was greatest) than in mice that received either carbon black only or carbon black 4 weeks after bleomycin (~1 mg). The unexposed mice and those treated with bleomycin only had approximately 0.2 mg of insoluble residue. This study shows that the retained lung dose of carbon black can increase significantly during a condition of pulmonary inflammation and epithelial cell injury.

(c) Comparison of clearance and retention of carbon black in lungs of three rodent species

The lung retention of and response to inhaled carbon black particles (Printex 90 and Sterling V) were investigated in three rodent species: Fischer 344 rats, B6C3F$_1$ mice and 276 F1B Syrian hamsters (all females) (Elder *et al*., 2005). The Printex 90 had a primary particle size of 14 or 17 nm (both were reported), a specific surface area of 300 m^2/g and an MMAD of 1.4–2.0 μm (GSD, 2.3–2.8) for the various exposure chambers by rodent

species and exposure group. The Sterling V had a primary particle size of 70 nm, a specific surface area of 37 m^2/g and an airborne particle size of 0.8 μm MMAD (GSD, 3.2). Printex 90 was labelled as a high-surface area carbon black, while Sterling V was labelled as low-surface area carbon black. Rats were exposed to low, medium and high concentrations of Printex 90 of approximately 1, 7 and 50 mg/m^3 for each species, respectively, for 6 hours per day on 5 days per week for 13 weeks. In addition, rats only were exposed to Sterling V at a concentration of approximately 50 mg/m^3. Five or six animals were used per exposure group. The study was designed to provide the same dose, as either mass or surface area, for the two types of carbon black studied. Thus, although the mass doses were different, similar surface area doses were achieved in the rat lungs from exposure to 7 mg/m^3 Printex 90 and to 50 mg/m^3 Sterling V, i.e. approximately 0.3 m^2 (Elder *et al*., 2005). Although the surface area doses were different, similar mass doses were achieved at 50 mg/m^3 Printex 90 or Sterling V, i.e. approximately 5.5 mg or 8 mg, respectively. Particle retention in the lungs was observed to be prolonged after exposure to the mid-(7 mg/m^3) and high (50 mg/m^3) concentrations of Printex 90 in rats and mice, and also for 50 mg/m^3 Sterling V in rats. In hamsters, which had the most efficient clearance, pulmonary retention was prolonged only at the high dose.

(d)   Translocation of carbon black particles from the site of deposition to other tissues

Female Swiss mice, aged 4 weeks and 18 months, were given with 7 mg ^{7}Be-labelled furnace black particles (Elftex 8) by gavage. The distribution of the isotope was determined in the animals 4 hours and 1, 2, 5 and 14 days after exposure. The authors concluded that there was uptake and distribution from the gut and that transit was more rapid in young mice. Peyer's patches (a gut-associated lymphoid tissue) of older mice took up more radiolabel than those of younger mice (LeFevre & Joel, 1986). [It was not clear from the study whether the authors verified the stable binding of the radiolabel to the particles.]

In a study of ultrafine carbon black and other particles instilled in rat lungs, Oberdörster *et al*. (1992) determined that the translocation of particles from the alveolar lumen of the lungs was dependent on particle size. Following intratracheal instillation of 0.5 mg particles of different sizes, the smaller ultrafine particles (12 and 20 nm) penetrated the alveolar epithelial cell barrier and entered the lung interstitium to a greater extent than an equal mass of larger respirable particles (> 200 nm) within 24 hours. This proportion was shown to increase with increasing particle dose as either mass or surface area.

More recent studies have shown that ultrafine carbon and other particles can translocate beyond the lungs. Oberdörster *et al*. (2002) showed that inhaled spark-generated ultrafine ^{13}C-carbon particles of approximately 25 nm in diameter were cleared rapidly from rat lungs and translocated to other organs (e.g. liver and spleen). Significant amounts of particles were found in the livers of rats in the high-exposure group (approximately fivefold higher amounts in the liver than in the lung at 24 hours).

Clearance or translocation from the lungs may also depend on the composition of the particle. For example, ultrafine iridium particles inhaled by rats for 1 hour remained in the lungs to a much greater extent and only a small proportion was cleared (< 1% in 7 days) (Kreyling *et al*. 2002). However, of the iridium particles that did translocate from the lungs, 10 times more 15-nm particles translocated than 80-nm particles. In another study in rats, inhaled ultrafine elemental silver particles were found to enter the blood circulation (Takenaka *et al*., 2001).

Inhalation of ultrafine particles may also result in translocation of particles to the brain. Ultrafine insoluble ^{13}C-carbon particles (CMD, 36 nm; GSD, 1.66) were found in the brains of Fischer 344 rats on days 1–7 following a 6-hour inhalation exposure to 160 μg/m^3 (Oberdörster *et al*., 2004). Approximately 50% of the inhaled ultrafine particles was predicted to deposit in the olfactory mucosa (assuming equal distribution) of rats and approximately 20% of that amount was found in the olfactory bulb. On day 1 after exposure, 0.35 μg/g of added ^{13}C was detected in the olfactory bulb; the amount increased on days 3 and 5 after exposure and reached 0.43 μg/g on day 7. The cerebrum and cerebellum contained significantly increased concentrations of ^{13}C on day 1, but the levels tended to decrease subsequent to exposure. The study was not designed to distinguish between the possible paths through which ^{13}C ultrafine particles could reach the brain, including crossing the blood–brain barrier (by particles that translocated into the blood following deposition anywhere in the respiratory tract) and transport of particles that deposited in the nasal olfactory mucosa along the olfactory nerve to the olfactory bulb. However, the authors concluded that the olfactory nerve pathway was the most probable explanation for the ^{13}C found in the olfactory bulb because of the significant increase in amounts in that region and the consistency with previous studies that demonstrated an olfactory nerve pathway for ultrafine particles (Bodian & Howe, 1941; De Lorenzo, 1970). Studies in non-human primates have demonstrated the translocation of 30-nm viruses and 50-nm gold particles from the nasal region to the olfactory bulb of the brain. Hunter and Dey (1998) reported another pathway through which particles may enter the central nervous system, via the trigeminal nerve, which has synaptic innervation in the nasal epithelium.

The size of individual ultrafine particles may allow their entry into cells and cellular organelles more readily than larger particles or agglomerates. In a study of concentrated particles from air pollution (including carbon particles) in human bronchial epithelial cells and mouse alveolar macrophages, the ultrafine fraction (< 100 nm) was found to penetrate the cells, localize in mitochondria and cause oxidative damage to mitochondrial membranes (Li *et al*., 2003).

(e)   *Kinetics of carbon black-adsorbed material*

Concern had been raised that material, including carcinogenic compounds, adsorbed onto carbon black particles are retained longer in the lung upon inhalation and will subsequently lead to a greater availability of carcinogens to target cells in the lung. In particular, this would be of importance for materials such as diesel exhaust particles,

which are known to contain PAHs adsorbed onto the carbon core and which may contribute to the carcinogenic response of inhaled diesel exhaust. These studies are summarized in Table 4.2.

Pylev *et al*. (1970a,b) instilled [^{3}H]benzo[*a*]pyrene adsorbed onto furnace black particles (26–160 nm) intratracheallly into Syrian hamsters and followed retention of radioactivity for 21 days. Compared with [^{3}H]benzo[*a*]pyrene suspended in aminosol vitrum, retention of [^{3}H]benzo[*a*]pyrene was longer when adsorbed onto carbon black (Pylev *et al*., 1970b).

In another study, male Fischer 344/Crl rats were exposed by inhalation for 30 days to Elftex 12 (furnace black; primary particle size, 37 nm; surface area, 43 m^2/g) with adsorbed [7-^{14}C]benzo[*a*]pyrene (Sun *et al*., 1989) or [4,5,9,10-^{14}C]-1-nitropyrene (Wolff *et al*., 1989). A total concentration of 100 mg/m^3 was used with the addition of either 0.2, 2 or 20% benzo[*a*]pyrene or 2 mg/m^3 1-nitropyrene. The long-term retention of radioactivity from both benzo[*a*]pyrene and 1-nitropyrene was increased when adsorbed onto carbon black. For both adsorbed compounds, a biphasic clearance was found, and most radioactivity was cleared from the lungs within 1–2 days. At all time-points, 16–60 times more radioactivity was retained after treatment with the adsorbed compounds compared with administration of the pure compound. Covalent interaction of these compounds with lung macromolecules was also greater when they were co-administered with carbon black particles.

These studies demonstrate that carbon black administered to rats and hamsters either by inhalation or intratracheal instillation can act as a carrier of adsorbed material, which is subsequently cleared from the lung much more slowly than the material given alone. In another study, Buddingh *et al*. (1981) reported that benzo[*a*]pyrene was poorly eluted from carbon black *in vitro* by human plasma or by swine serum, swine lung washing or lung homogenate, which is consistent with the findings of Borm *et al*. (2005) in surfactant-containing saline solution using four different carbon blacks.

4.1.3   *Dosimetry models in humans and rodents*

Dosimetry models can be used to estimate the particle dose in a given region of the respiratory tract for any given exposure. The development, calibration and validation of these models depend on the availability of experimental data and the models can be further validated and refined as additional studies become available.

Differences in the kinetics of particle clearance and retention in rodents and humans have been taken into account, to the extent of available data, in species-specific models of particle deposition and retention. Route of breathing affects the amount and site of deposition in the respiratory tract since the efficiency of nasal deposition generally exceeds that in the oral passage (Oberdörster, 1988). In a comparison of predictions from rat and human models in the multiple path particle deposition model (CIIT & RIVM, 2002), Brown *et al.* (2005) determined that the exposure to airborne particles would

Table 4.2. Kinetics of carbon or carbon black (CB)-adsorbed compounds

Characteristics of carbon black	Adsorbed compound	Test system	Duration	End-points	Findings	Reference
Furnace black 26–160 nm	[^{3}H]BaP	Intratracheal instillation; Syrian hamster	21 days	Macrophage response and BaP retention	CB + BaP elicited more macro-phages; longer BaP retention with CB than without	Pylev *et al.* (1970a,b)
Elftex 12 (furnace black) 37 nm; 43 m^2/g	^{14}[C]BaP	Inhalation; Fischer 344/N rat; 100 mg/m^3 mass with 0.2, 2 or 20% BaP; BaP alone, 2, 20 mg/m^3; intratracheal instillation of 500 μg CB±10 or 100 μg BaP	2 h exposure (nose only) + 30 days	BaP lung retention	Biphasic lung retention; long-term retention of BaP increased 16–60 times when coated onto CB; more pronounced after instillation compared with inhalation	Sun *et al.* (1989)
Elftex 12 (furnace black) 37 nm; 43 m^2/g	^{14}[C]-1-Nitro-pyrene	Inhalation; Fischer 344/N rat; 98 mg/m^3 CB+2 mg/m^3 nitropyrene; nitropyrene alone	2 h exposure (nose only) + 30 days	Nitropyrene lung retention	Biphasic nitropyrene retention increased when adsorbed onto CB	Wolff *et al.* (1989)

BaP, benzo[*a*]pyrene

CARBON BLACK

generally need to be higher in rats to result in doses equivalent to those in human lungs, the extent of which depends on the particle characteristics and breathing patterns.

In humans, several models of particle deposition have been developed and evaluated (e.g. ICRP, 1994; NCRP, 1997; CIIT & RIVM, 2002). Studies on particle clearance and retention in human lungs have been more limited. Martonen *et al*. (2005) have provided an overview of models of human lung deposition and clearance that have been developed over the years.

Several models of particle deposition and clearance in rat lungs have been developed (e.g. Strom *et al.*, 1989; Yu *et al.*, 1989; Stöber *et al*., 1990; Yu & Rappaport, 1997; Stöber, 1999; Tran *et al*., 1999, 2000; CIIT & RIVM, 2002), some of which describe the rat alveolar region as a single compartment with dose-dependent clearance rate coefficients (Yu *et al*., 1989; Yu & Rappaport, 1997; CIIT & RIVM 2002), while others include additional compartments for the interstitial transport or sequestration of particles (free or phagocytosed) and dose-dependent clearance (Strom *et al*., 1989; Stöber *et al*., 1990; Stöber, 1999; Tran *et al*., 1999, 2000).

Two recent studies that compared the long-term retention kinetics of particles in rats and humans used data from coal miners in the United Kingdom and in the USA that included work histories and estimates of exposure to respirable particles and retained mass of coal and silica in the lungs and hilar lymph nodes (Kuempel, 2000; Tran & Buchanan, 2000; Kuempel *et al*., 2001). A model of lung deposition and clearance in rats was found to underpredict the retained lung burdens of particle mass in coal miners who had had lower lifetime exposures and to overpredict those of coal miners who had had high exposures. At low exposures, the rat model is a simple, first-order kinetic model that predicts effective clearance and very little particle retention in the lungs of retired miners. At high exposures, the rat model predicts impaired clearance and much higher retained burdens than those actually observed in coal miners. A human model that incorporates the concept of slow clearance (with three first-order compartments and slow-to-very slow clearance rate coefficients) (ICRP, 1994) improve the fit to the data from coal miners. However, the model structure that was required to predict adequately the retained dust burden was a higher-order model with an interstitial or sequestration compartment (Kuempel *et al*., 2001). Within this model structure, rat-based overload kinetics did not improve the fit of the data, although a lesser degree of overloading could not be ruled out. The model structure with an interstitial or sequestration compartment is consistent with the observations of little or no particle clearance from the lungs of retired miners (Freedman & Robinson, 1988) and with the retention of particles in the interstitium of human lungs (Nikula *et al*., 2001). It is also consistent with the structure of some of the animal models (Strom *et al*., 1989; Stöber *et al*., 1990; Stöber, 1999; Tran *et al*., 1999, 2000).

An area for further development in each of these mass-based models of animal and human lung dosimetry is the fate of inhaled ultrafine particles. Particle size-selective clearance is included in current models to the extent that the particle size influences the site of deposition in the respiratory tract; also, the mechanisms of biological clearance

depend on the specific region of the respiratory tract. However, experimental studies (see Section 4.1.2) have shown that the fate of inhaled ultrafine particles may differ considerably from that of larger respirable particles of the same composition, and may include translocation within lung tissues and beyond the respiratory tract.

4.2   Toxic effects

4.2.1   *Humans*

Comprehensive reviews of the toxicity of carbon black to humans are available (National Institute for Occupational Safety and Health, 1978; Rivin & Smith, 1982; IARC, 1984; Gardiner, 1995; IARC, 1996).

(a)   *Observations in the general population*

Chest radiographic features of small opacities that are consistent with pneumoconiosis have been observed in the general population. An analysis of nine study populations reported prevalences of small opacities (International Labour Organization (ILO) grade 1/0 or greater) ranging from 0.21 to 11.7%. A meta-analysis of these data yielded a population prevalence of 5.3% (95% CI, 2.9–7.7%). The prevalence was significantly greater in Europe (11.3%; 95% CI, 10.1–12.5%) than in North America (1.6%; 95% CI, 0.6–2.6%), which could not be explained on the basis of age, gender or smoking history. There was a greater prevalence of lung opacities in men (5.5%; 95% CI, 3.4–7.6%) than in women (3.5%; 95% CI, 1.3–5.8%). The age-specific pooled prevalence was higher in the study populations with a mean age of ≥ 50 years than in those with a mean age of < 50 years in both Europe (11.7% versus 9.6%) and North America (2.3% versus 0.6%). Environmental and unaccounted occupational exposures as well as reader variability may play a role in the determination of the prevalence of small opacities in these subjects and may explain the large differences between different regions (Meyer *et al*., 1997).

(b)   *Respiratory effects in carbon black workers*

Gärtner and Brauss (1951) first described radiological changes analogous to pneumoconiosis in 31 workers in a carbon black factory. However, these individuals had no lung function abnormality. Since that time, a series of other reports have been published on pneumoconiosis in carbon black workers.

A health survey was conducted in two German factories that produced carbon black from acetylene or from oil that was burned with light gas, respectively. Among 56 workers, 16 had been employed for more than 10 years. Two of these workers had chest X-ray changes compared with none of the 52 controls who had had radiographs taken without suspicion of lung disease (von Mai, 1966). [The selection of workers was not clear, neither were the criteria for diagnosis.]

Most studies of respiratory morbidity have methodological shortcomings or provide insufficient detail for a reliable interpretation of the results (see review by Gardiner,

148   IARC MONOGRAPHS VOLUME 93

1995). Nevertheless, exposure–response relationships were evident for symptoms of chronic bronchitis, small opacities on chest radiographs and several respiratory parameters (forced expiratory volume in 1 second [FEV_1], $FEF_{25-75\%}$). Studies in Germany (Küpper *et al*., 1996) and Poland (Szozda, 1994, 1996) provided evidence of a relationship between exposure to carbon black and lung function among smokers. The Polish studies also reported cases of hypertension and pneumoconiosis among carbon black workers.

Spirometry, body plethysmography and inhalation challenge tests were conducted among employees at a German carbon black production plant to assess the impact of fine carbon black dust on pulmonary function, to determine the prevalence of obstructive airway disease among the workers and to investigate whether exposure to fine dust is related to the prevalence of bronchial hyper-responsiveness. A total of 573 exposed workers (178 nonsmokers, 107 former smokers, 288 smokers) and 99 controls (46 nonsmokers, 13 former smokers, 40 smokers) participated in the study. Measurements of dust in air showed concentrations of 0.01–9.14 mg/m^3 for fine dust (9–200 nm [includes fine and ultrafine sizes]) and 1.08–19.95 mg/m^3 for total dust (mean dust concentrations, 0.58 mg/m^3 for respirable dust; 1.08 mg/m^3 for inspirable dust). Exposure to carbon black had a small but statistically significant impact on lung function in smokers ($P < 0.01$). Nevertheless, exposed smokers displayed signs of obstructive airway disease more frequently (7.3%) than exposed nonsmokers (3.9%). There was no effect of exposure to carbon black on lung function in former smokers or nonsmokers. Exposure to carbon black dust was not associated with an increased prevalence of bronchial hyper-reactivity (Küpper *et al*., 1996).

To investigate the occurrence of medical conditions related to exposure to carbon black, a large study was conducted in 18 carbon black production plants (including the German plant; Küpper *et al*., 1996) in seven European countries between mid-1987 and mid-1989. A total of 1298 respirable [SIMPEDS cyclone method] and 1317 total inhalable [Institute of Occupational Medicine head method] samples were taken and included in the study. The distributions of the TWA values were best described by a log-normal distribution and exposure was characterized by GMs and standard deviations (Gardiner *et al*., 1992b). In a subsequent study, exposure-related health effects were assessed in 3086 employees in these plants through respiratory health questionnaires, spirometry and chest radiographs. Personal monitoring was used to measure current exposure to inhalable and respirable carbon black, sulfur dioxide and carbon monoxide. The final analysis comprised 1742 employees in 15 plants (81% response rate) who provided data on respiratory symptoms and spirometry, and 1096 chest radiographs were available from 10 plants (74% response rate). In addition to the respirable (1298) and inspirable (total inhalable; 1317) dust samples mentioned above, 1301 sulfur dioxide and 1322 carbon monoxide samples were also collected. This study thus included a comprehensive assessment of current occupational exposure to carbon black dust and its associated gaseous contaminants. In respirable dust samples, the geometric mean level was 0.21 (GSD, 2.7) mg/m^3 and in total inhalable dust, the GM level was 0.57 (GSD,

4.0) mg/m^3. Associations were found between cough, sputum production, the symptoms of chronic bronchitis (mean prevalence, 10%) and indices of increasing current exposure (from 0.14 to > 0.45 mg/m^3). There was a small reduction in lung function with increasing dust exposure in both smokers and nonsmokers. Nearly 25% of the chest radiographs showed small opacities (ILO category 0/1 or greater), which were strongly associated with indices of cumulative dust exposure, after accounting for production plant and current smoking habits. The findings were consistent with a non-irritant effect of carbon black dust on the airways combined with dust retention in the lungs (Gardiner *et al*., 1993).

Chronic inflammation has also been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom (1991) found a statistically significant increase in the percentage of polymorphonuclear neutrophils in the bronchoalveolar lavage (BAL) fluid of workers with respiratory impairment who had been exposed to asbestos, coal or silica (4.5% in cases versus 1.5% in controls). Elevated levels of such cells have been observed in the BAL fluid of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3.4% in controls; Vallyathan *et al*., 2000) and in patients with acute silicosis (a 10-fold increase over controls; Goodman *et al*., 1992; Lapp & Castranova, 1993).

The results of two additional studies (phases 2 and 3) of respiratory health of European carbon black workers showed exposure-related adverse effects of carbon black on the respiratory system, which were evident from an increase in the prevalence of cough and sputum production, and reductions in lung function, based on measurements of FEV_1, $FEF_{25-75\%}$ and the FEV_1/forced vital capacity (FVC) ratio. An increase in exposure to inhalable dust of 1 mg/m^3 was associated with an increase of 80% in the prevalence of respiratory symptoms of chronic bronchitis (odds ratio, 1.8; 95% CI, 1.3–2.6) in phase 2, but not in phase 3. The prevalence of respiratory symptoms such as cough and cough and sputum production, however, was significantly affected by an increase of 1 mg/m^3 in exposure. Working for 40 years with a mean exposure of 1 mg/m^3 (480 mg.month/m^3) was expected to increase the prevalence of cough by almost 70% (odds ratio, 1.7; 95% CI, 1.2–2.1) and that of cough and sputum production by 60% (odds ratio, 1.6; 95% CI, 1.2–2.1). Similarly, a 1-mg/m^3 increase in exposure to carbon black was associated with significant decrements in FEV_1, $FEF_{25-75\%}$ and FEV_1/FVC ratio (Gardiner *et al*., 2001).

Van Tongeren *et al*. (2002) carried out a longitudinal analysis of workers in the European carbon black manufacturing study who had provided a full-size chest radiograph in each of the three cross-sectional surveys between 1987 and 1995. All chest radiographs were read independently according to the ILO classification by three experiences readers who were blind to all factors, including the sequence in which the chest radiographs were taken. After exclusion of all workers from a factory that had a low participation rate (< 60%) in the first survey and all workers who had reported various lung injuries, operations or respiratory disease (asthma, pleurisy or pulmonary tuberculosis), data from 675 employees were available for analysis. The prevalence of small opacities with ILO category $\geq$ 1/0 was 13.9, 19.9 and 19.7% in the first, second and third survey, respectively. An association between cumulative exposure during the study

and progression of small opacities was observed, although only four cases of existing small opacities ($\geq 1/0$) in the first survey progressed to higher ILO categories. The authors concluded that exposure to carbon black was associated with the incidence of small opacities, although this effect may be reversible after cessation of exposure.

Harber *et al.* (2003) investigated whether exposure to carbon black was associated with decrements in lung function and increased prevalence of respiratory symptoms among 1755 employees from 22 North American carbon black manufacturing plants. Multiple linear regression analyses showed that cumulative exposures to 'total' and inhalable dust were both was associated with a statistically significant decrement in FEV_1 and with FVC. The slopes were –2 mL and –0.7 FEV_1/mg–year/m^3 for cumulative exposure to 'total' and inhalable dust, respectively. Cumulative exposure was also associated with an increased prevalence of chronic bronchitis in nonsmokers.

4.2.2   *Experimental systems*

(a)   *Inhalation exposure*

The effects of subchronic inhalation of carbon black on pulmonary inflammation, expression of inflammatory cytokines and growth factors, and on lung histopathology were studied in male Fischer 344 rats exposed for 6 hours per day on 5 days per week for up to 13 weeks to 1.1, 7.1 and 52.8 mg/m^3 carbon black (Monarch 880, Cabot; diameter, 16 nm; surface area, 220 m^2/g). Effects on the lung were assessed after 6.5 and 13 weeks of exposure and after 3 and 8 months of recovery. After 13 weeks, lung burdens were 354, 1826 and 7861 µg carbon black at the three exposure concentrations, respectively. Inhalation of 1.1 mg/m^3 carbon black did not cause any of the adverse effects on the lung that were measured, but lung clearance appeared to be impaired after exposure to 7.1 and more severely so after exposure to 52.8 mg/m^3. Analysis of BAL fluid showed no effect of the lowest dose and a relative increase in the number of neutrophils after exposure to the intermediate dose that persisted. At the highest dose of carbon black, an increase in total cell number and neutrophils and a decrease in macrophages were observed. The BAL fluid concentrations of lactate dehydrogenase, β-glucuronidase and total protein were also increased at this dose. All these effects persisted until 8 months after exposure. mRNA expression of macrophage inflammatory protein 2 (MIP-2) and monocyte chemotactic protein 1 (MCP-1)—two chemotactic cytokines—was minimal in the lungs of rats in the low-dose group, but MIP-2 mRNA was clearly present at all time-points after exposure to 7.1 and 52.8 mg/m^3. MCP-1 mRNA was also increased at these doses, but this effect was persistent for up to 8 months after exposure to the high dose only. In lung tissue sections, particle-containing macrophages were seen in alveolar and alveolar duct regions after the 1.1-mg/m^3 dose. The intermediate dose produced acute inflammation (characterized by accumulation of neutrophils and macrophages within alveolar spaces), mild epithelial hyperplasia and mild interstitial fibrosis. The 52.8-mg/m^3 dose caused mainly lesions in the alveolar ducts, with pronounced epithelial hyperplasia and fibrosis. Alveolar type II cell hypertrophy and hyperplasia seen after exposure to

intermediate and high doses persisted throughout the 8-month recovery period (Driscoll *et al*., 1996).

To investigate whether the inflammatory response induced by inhaled ultrafine particles involves an increased release of systemic clotting factor, adult male Wistar rats were exposed by inhalation for 7 hours to fine or ultrafine carbon black particles. The attained total suspended particle concentrations were 1.66 mg/m^3 for ultrafine (Printex 90; diameter, 14 nm) and 1.40 mg/m^3 for fine carbon black (Huber 990; diameter, 260 nm). Particle concentration (number of particles/m^3) of the ultrafine carbon black was more than 10 times greater than that of the fine particles; the average CMDs were 114 nm for ultrafine and 268 nm for fine carbon black. Exposure to ultrafine particles caused an increase in total cell number and in the number of neutrophils in BAL fluid immediately after exposure. Both fine and ultrafine carbon black caused twofold and fourfold increases, respectively, in the number of polymorphonuclear leukocytes in BAL 16 hours after exposure. Exposure to ultrafine but not to fine carbon black particles was associated with a significant increase in the total number of blood leukocytes. Blood coagulation-related plasma, fibrinogen, factor VII and von Willebrand factor were all unaffected by exposure to particles. MIP-2 mRNA was significantly increased in BAL cells 48 hours after the end of exposure to ultrafine carbon black. The data showed a small but consistent pro-inflammatory effect of ultrafine particles that was greater than that of the same exposure (on a weight/volume basis) to fine carbon black (Gilmour *et al*., 2004).

The retention kinetics, inflammation and histopathology following exposure to carbon black were examined in female Fischer 344 rats, B6C3F$_1$ mice and F1B Syrian golden hamsters exposed to 0, 1, 7 and 50 mg/m^3 (nominal concentrations) carbon black particles (Printex 90; diameter, 14 nm; surface area, 300 m^2/g) for 6 hours per day on 5 days per week for 13 weeks. Rats were also exposed to 50 mg/m^3 (nominal) low-surface area carbon black (Sterling V; diameter, 70 nm; surface area, 37 m^2/g). Retention and effects were measured immediately after exposure and 3 and 11 months later; retention was also evaluated after 5 weeks of exposure. Significant decreases in body weight were observed only in hamsters exposed to the high dose of carbon black. Lung weights were increased in all groups exposed to this dose, but this persisted only in rats and mice up to 11 months after exposure. Lung inflammation and histopathology (lung lesions located primarily in the centriacinar regions, with the most extensive epithelial and inflammatory responses in the alveolar ducts and surrounding parenchyma) were more severe and prolonged in rats than in mice and hamsters, and were similar in rats exposed to 'surface-area equivalent' concentrations of 7 mg/m^3 Printex 90 and 50 mg/m^3 Sterling V. Hamsters had the most efficient clearance and least severe responses of the three species. The results obtained in rats suggest that the surface area of the particles is an important determinant of dose to the target tissue and subsequent effects (Elder *et al*., 2005).

(b)   Intratracheal or intranasal instillation

Respiratory syncytial virus causes bronchiolitis and pneumonia in infants and may lead to the development of asthma in childhood. To determine whether exposure to

particles modulates the immune response to this virus, 8-week-old female BALB/c mice received an intratracheal instillation of 40 μg ultrafine carbon black particles (150 m^2/g) in 100 μL saline. The following day, mice were instilled with either 10^6 plaque-forming units of respiratory syncytial virus or uninfected medium. Compared with animals that received the virus alone, tumour necrosis factor-α (TNFα) protein was reduced in the BAL fluid on days 1 and 2 of infection in mice exposed to both carbon black and the virus. There was a reduction in the number of lymphocytes in the BAL fluid on day 4, and decreased levels of interferon (IFN)-γ-inducible protein lymphotactin and IFN-γ mRNAs in the lungs of mice exposed to carbon black plus virus. On days 2–4 of infection, viral titres in these mice were lower than those in animals that had received respiratory syncytial virus alone. By day 7, however, the numbers of neutrophils, expression of pro-inflammatory cytokine mRNA, TNF-α and Th2 cytokine interleukin (IL)-13 protein levels were increased in the lungs of mice exposed to carbon black plus virus, which indicated an exacerbation of infection. The data showed that pre-exposure to ultrafine particles induces an inflammatory condition that promotes Th2-type immune responses rather than the production of IFN-γ Th1, which is necessary for microbial defence (Lambert *et al*., 2003).

The ability of ultrafine and fine particles to induce inflammation, cause epithelial injury and affect alveolar macrophage clearance (phagocytosis, chemotaxis) was studied in Wistar rats instilled with 125 or 500 μg fine titanium dioxide (mean diameter, 250 nm; 6.6 m^2/g), ultrafine titanium dioxide (mean diameter, 29 nm; 49.8 m^2/g), fine carbon black (Huber 990; mean diameter, 260.2 nm; 7.9 m^2/g) or ultrafine carbon black (Printex 90; mean diameter, 14.3 nm; 253.9 m^2/g) in 0.5 mL saline. Inflammation was quantified by counting the number of neutrophils in BAL fluid. The ultrafine particles recruited more polymorphonuclear neutrophils, caused more epithelial damage and were more cytotoxic than fine particles at equal mass concentrations. Both ultrafine and fine particles significantly impaired the ability of alveolar macrophages to phagocytose fluorescent indicator beads, but only treatment with ultrafine particles enhanced the C5a-stimulated chemotactic potential of the macrophages. This study showed that ultrafine particles [of two very different materials] induced inflammation and epithelial damage to a greater extent than their larger-sized mass counterparts. In general, the effect of ultrafine carbon black was greater than that of ultrafine titanium dioxide, which suggests that there are differences in the potential hazard of different types of ultrafine particle. Epithelial injury and toxicity were associated with the inflammatory response that followed exposure to ultrafine particles. Increased sensitivity to a C5a chemotactic stimulus as a result of exposure to ultrafine particles could retain the macrophages in the lung at the site of particle deposition, and thus allow the dose to accumulate (Renwick *et al*., 2004).

To explore the role of vascular endothelial growth factor (VEGF) in the induction of alveolar capillary permeability by ultrafine particles, male ICR mice received an intratracheal instillation of 200 μg carbon black (Printex 90; diameter, 14 nm before grinding; surface area, 253.9 m^2/g). A significant and sustained increase in total proteins was observed in BAL fluid, which was maximal at 21 hours after instillation. The level of

TNFα was significantly elevated only at 4 hours, but significant increases in VEGF were seen throughout the 42-hour study period, with a peak increase at 16 hours. The results showed that ultrafine carbon black particles induce the production of VEGF, which is associated with an increase in alveolar capillary permeability. The involvement of oxidative stress in this process was supported by the observation in an in-vitro study that *N*-acetylcysteine (a scavenger of reactive oxygen species) prevents the induction of VEGF by ultrafine carbon black particles (Chang *et al*., 2005).

The kinetics of airway toxicity or inflammation and allergic sensitization to ovalbumin in response to ultrafine carbon black particles (diameter, 30–50 nm) was studied in BALB/cANNCrl mice exposed intranasally to ovalbumin (10 μg in 20 μL) alone or in combination with 2, 20 or 200 μg carbon black particles. Airway toxicity and inflammation were assessed on days 4 and 8, immune adjuvant effects were measured in the lung-draining peribronchial lymph nodes on day 8, antigen-specific immunoglobulin E (IgE) was measured on days 21 and 28 and allergic airway inflammation was studied after ovalbumin challenges on day 28. The dose of 200 μg carbon black particles, but not 20 μg or 2 μg, induced immediate airway inflammation and had immune adjuvant activity that involved enlargement of the peribronchial lymph nodes and an increased ovalbumin-specific production of Th2 cytokines IL-4, IL-5 and IL-10. Serum levels of ovalbumin-specific IgE were increased on day 21, which was indicative of systemic sensitization. This was supported by allergic airway inflammation after challenges with ovalbumin. The authors concluded that there is a correlation between early airway toxicity and adjuvant effects of carbon black particles and that local cytokine production early after exposure to these particles is predictive of airway inflammation (de Haar *et al*., 2005).

The size-specific effects of particles on pulmonary immune response, translocation to lymph nodes and expression of chemokine mRNA were studied in the lung and lymph nodes of 8-week-old male BALB/c mice exposed to ultrafine or fine carbon black particles by intratracheal instillation. In a first experiment, 25, 125 or 625 μg ultrafine carbon black particles (Printex 90; diameter, 14 nm; 300 m^2/g) were administered once a week for 4 weeks. In a second experiment with the same dose regimen, larger-sized carbon black (Flammruss 101; diameter, 95 nm; 20 m^2/g) was instilled. Total and differential cell counts and release of cytokines and chemokines were measured in BAL fluid 24 hours after the last instillation. In a third experiment, a dose of 125 μg ultrafine carbon black or larger-sized carbon black was administered according to the same schedule, and lungs and mediastinal lymph nodes were isolated 4 hours after the last instillation to measure expression of chemokine mRNA. The total cell count and differential cell counts (macrophages, lymphocytes, neutrophils) in BAL fluid increased significantly in mice exposed to the ultrafine carbon black particles in a dose-dependent manner, as did the release of IL-1β, IL-6 and TNFα. MIP-1 α/CCL-3 protein and mRNA expression were also increased in the lungs and lymph nodes of these mice. The effects seen with the 95-nm carbon black particles were weaker than those obtained with the smaller-sized particles. Particle translocation to the mediastinal lymph nodes was greater in mice given the ultrafine particles than in those that received the larger-sized carbon

black. The study showed that repeated intratracheal instillation of ultrafine carbon black particles in mice leads to pulmonary inflammation, translocation of particles to mediastinal lymph nodes and enhanced expression of chemokine mRNA in the lung and lymph nodes. These effects were stronger with ultrafine than with fine particles (Shwe *et al*., 2005).

The effects of ultrafine and fine particles on immune function in the mouse brain were investigated by the instillation of 125 μg carbon black (Printex 90; diameter, 14 nm; 300 m^2/g; or Flammruss 101; diameter, 95 nm; 20 m^2/g) into the nostrils of 8-week-old male BALB/c mice once a week for 4 weeks. Four hours after the last instillation, the olfactory bulb and hippocampus were isolated. The mRNA expression of pro-inflammatory cytokines (IL-1β and TNFα) and chemokines (MCP-1/CCL2, MIP-1α/CCL3) and monokine-induced INF-γ /CXC chemokine ligand was enhanced in the brain olfactory bulb but not in the hippocampus of mice instilled with 14-nm carbon black particles. The 95-nm particles did not show effects in either organ at the doses used (Shwe *et al.*, 2006).

Yang *et al*. (1999) tested the combined effect of particulates and organic compounds on the alveolar macrophage response to bacteria or bacterial products (such as lipopolysaccharide) and the secretion of pro-inflammatory cytokines (IL-1 and TNFα). A comparative study of the pulmonary responses to exposure to diesel exhaust particles, carbon black and silica was conducted in male Sprague-Dawley rats that were exposed to a single intratracheal dose (5 or 35 mg/kg bw) of diesel exhaust particles (NIST; MMAD, 0.5 μm), carbon black (Elftex 12 furnace black; MMAD, 0.1–0.6 μm), silica (Min-U-Sil; MMAD, < 5 μm) or saline. The alveolar macrophages isolated from the particle-exposed rats were challenged *ex vivo* with lipopolysaccharide (0.1 μg/10^6 alveolar macrophages) and cytokines were monitored. In addition, rats were exposed to a single dose of diesel exhaust particles (5 mg/kg bw) followed 3 days later by exposure to lipopolysaccharide (1 mg/kg bw) for 3 hours *in vivo*. Exposures to diesel exhaust particles, carbon black and silica resulted in polymorphonuclear neutrophil infiltration and elevated levels of albumin and lactate dehydrogenase in the BAL fluid. The alveolar macrophages from the carbon black- and silica-exposed rats showed an increased production of TNFα but not of IL-1 and did not show a decreased response to a subsequent challenge with lipopolysaccharide. Upon *ex-vivo* challenge with lipopolysaccharide, the alveolar macrophages from diesel exhaust particle-exposed rats showed a significant decrease in TNFα. The authors concluded that diesel exhaust particles, carbon black and silica all induced a pulmonary response due to particle stimulation, but only diesel exhaust particles suppressed cytokine release in alveolar macrophages in response to stimulation with lipopolysaccharide.

Nilsen *et al*. (1997) studied the adjuvant activity of diesel exhaust particles (NIST 1650; MMAD, 0.03 μm; 64 m^2/g) and carbon black (Regal 250R; MMAD, 0.035 μm; 65 m^2/g) on systemic IgE production in ovalbumin-treated mice after intranasal administration. Female Balb/cA mice were immunized four times with ovalbumin (20 μg) alone or in combination with diesel exhaust particles (25 μg) or carbon black (25 μg). One and 2 weeks later, increased responses in both the number of responding animals and

serum IgE antibody were seen in the animals treated with ovalbumin and either of the particles; the activity of diesel exhaust particles was more pronounced than that of carbon black, which indicated that the organic matter adsorbed to the diesel exhaust particles and the non-extractable carbon cores were both responsible for the observed adjuvant effect.

Al-Humadi *et al*. (2002) exposed Brown Norway rats intratracheally to saline, carbon black or diesel exhaust particles at 5 mg/kg bw followed by exposure for 30 minute to ovalbumin (90 mg/m^3) or saline 1, 8, 18 and 29 days later. Exposure to diesel exhaust particles, carbon black or ovalbumin alone did not result in abnormal levels of inflammatory cells, lactate dehydrogenase or total protein in the BAL fluid. However the combinations of ovalbumin with diesel exhaust particles or carbon black increased these markers, and also the level of IL-4 mRNA in lung tissue and serum levels of ovalbumin-specific IgG and IgE.

The effect of acute exposure to diesel exhaust particles on phase I and phase II enzymes was investigated in rat lung. Intratracheal administration of these particles enhanced cytochrome P450 (CYP) 1A1 protein levels and enzyme activity one day after exposure; enzyme levels returned to control values after five days. Carbon black particles (35 mg/ kg bw) did not induce CYP1A1 protein or enzyme activity. However, both particle types (at 5 and 35 mg/kg bw) caused a significant decrease in CYP2B1 protein and enzyme activity at day 1, which was persistent up to day 7 with 35 mg/kg bw. Similarly, both treatments significantly attenuated glutathione *S*-transferase (GST)-Pi protein on day 1 after exposure and decreased the activities of GST and catalase on days 1 and 7. The diesel exhaust particles, but not carbon black, significantly induced quinone reductase activity on day 7. The authors suggested that diesel exhaust particles may induce CYP1A1 and quinone reductase enzymes by a chemical effect, while the carbonaceous core may be involved in the attenuation of CYP2B1, GST and catalase protein levels and enzyme activities (Rengasamy *et al*., 2003).

Zhao *et al*. (2004) evaluated the change in lung metabolic enzymes in response to concentrations of 35 mg/kg bw saline, diesel exhaust particles and carbon black intratracheally instilled into rats that were then killed 1, 3 or 7 days later. Metabolically activated fractions (S9) were extracted from control and exposed rat lungs. The mutagenic activity of 2-aminoanthracene, 2-aminofluorene, 1-nitropyrene and an organic extract of diesel exhaust particles was then determined in *Salmonella typhimurium* YG1024. The S9 from the control and exposed rats showed a dose-dependent increase in mutagenic activity of all four compounds. Compared with the saline control, the S9 from the carbon black-exposed rats was a less potent inducer of mutagenicity of 2-aminoanthracene. When inhibitors of CYP1A1 (α-naphthoflavone, 1 μM/plate) or CYP2B1 (metyrapone, 10 μM/plate) were added to the reaction mixture to monitor the involvement of CYP1A1 in S9 metabolic activity in the lung, α-naphthoflavone inhibited the metabolic activation of 2-aminoanthracene induced by S9 from carbon black-exposed rats to a lesser extent than the metabolic activity induced by S9 from rats exposed to saline and diesel exhaust particles. The rats exposed to both particle types revealed a significant change in phase I and II enzymes in the lungs, including CYP1A1, CYP2B1, GST and nicotinamide

adenine dinucleotide phosphate quinone-oxidoreductase (Rengasamy *et al*., 2003). The authors suggested that, after exposure to carbon black, the reduction in the constitutive enzyme CYP2B1 in the lung may play a role in the pulmonary handling of mutagenic agents (Zhao *et al*., 2004).

(c)   Other routes

The effect of ultrafine particles on the microcirculation in extrapulmonary organs was investigated in C57BL/6 mice that received intra-arterial infusions of 1×10^7 or 5×10^7 ultrafine carbon black particles (Printex 90; diameter, 14 nm; surface area, 300 m^2/g) suspended in 200 μL buffer containing 15% human albumin. Two hours after infusion, platelet– and leukocyte–endothelial cell interactions, sinusoidal perfusion, endothelial fibrin deposition and the phagocytic activity of Kupffer cells were analysed by intravital video fluorescence microscopy in the liver microvasculature. The particles induced accumulation of platelets in the hepatic microvessels, which was associated with pro-thrombotic changes on their endothelial surface. Accumulation of particles in the liver had a strong procoagulatory effect, but did not trigger an inflammatory reaction or induce microvascular or hepatocellular tissue injury (Khandoga *et al*., 2004).

The possible adjuvant effect of diesel exhaust particles (NIST; diameter, 30 nm; 64 m^2/g) and carbon black (Regal 250R; diameter, 35 nm; 60 m^2/g), which was used as a surrogate for a non-extractable core of diesel exhaust particles with a similar size and surface area, on the response to the allergen ovalbumin was studied in BALB/c mice. A footpad inoculation was followed by a popliteal lymph node assay and other immunotoxic evaluations, including the weight change of popliteal lymph nodes, cell numbers and proliferation and specific serum IgE anti-ovalbumin antibody levels. Carbon black, although less potent than diesel exhaust particles, exhibited a similar capacity to increase the local lymph node response and specific serum IgE response to ovalbumin. Both particles had a significant adjuvant effect on the local immune-mediated inflammatory response and systemic specific IgE response to allergen, which suggested that the non-extractable particle core contributed substantially to the adjuvant activity of diesel exhaust particles (Løvik *et al*., 1997).

(d)   Ex-vivo and in-vitro studies

In a study on the cytotoxicity of diesel exhaust particles, their phagocytosis and the resulting immune response, carbon black particles (FR103; diameter, 95 nm) that were included as a surrogate of the carbonaceous core of the diesel exhaust particles were reported to contain 1.5% of the PAH content of the diesel exhaust particles. Human bronchial epithelial cells (16HBE14o-) and human nasal epithelial cells in primary culture were exposed to the two particle types. Treatment with carbon black particles (10 μg/cm^2 for 48 hours; concentrations were expressed per square centimeter since the particles sediment rapidly onto the culture) stimulated the release of granulocyte macrophage

CARBON BLACK   157

colony-stimulating factor (GM–CSF) and IL-8, but to a lesser extent than diesel exhaust particles (Boland *et al*., 1999).

The expression of human leukocyte antigen-DR (HLA-DR) on the cell membrane of antigen-presenting cells is of major importance for the induction of an allergic response in the airways. Because environmental particulates may induce or enhance allergic sensitization, a study was conducted to investigate the potential of carbon black (Vulcan M; CMD, 90 nm), diesel exhaust particles and urban air particulates ($0.1–1000$ ng/cm^2) to induce the expression of HLA-DR in cultures of differentiated THP-1 human monocytes, which are used as a model for alveolar macrophages. The 'adjuvant' potential of the particles on IFN-γ, a known enhancer of HLA-DR, was also studied. The particles alone did not induce HLA-DR on the THP-1 cells after 48 hours of incubation. However, even at very low concentrations, carbon black (1 ng/cm^2 and above) and diesel exhaust particles (0.1 ng/cm^2 and above) interacted with IFN-γ (100 U/mL) to enhance HLA-DR expression up to 2.5-fold. This in-vitro finding suggests the existence of a mechanism by which particles exert an adjuvant activity and which may partially explain how exposure to particles can enhance allergic sensitization (Don Porto Carero *et al*., 2002).

The effects of 10, 20 or 30 μg/cm^2 ambient particulate matter, diesel exhaust particles and carbon black particles (FR103; diameter, 95 nm) on cultured human bronchial epithelial (16HBE14o-) cells were compared. No significant effects on cell viability were observed after incubation with either particle type. In contrast to ambient particulate matter and diesel exhaust particles, carbon black particles did not disturb cell growth or induce the production of peroxides or the release of GM–CSF. Carbon black particles were more actively phagocytosed than the two other particle types (Baulig *et al*., 2003a). In a subsequent study, the same carbon black particles (10, 20 or 30 μg/cm^2, equivalent to 50, 100 or 150 μg/mL) did not cause an increase in reactive oxygen species or induce the expression of CYP1A1 mRNA in 16HBE14o- cells, whereas diesel exhaust particles did (Baulig *et al*., 2003b).

In another study that compared the effects of various forms of diesel exhaust and carbon black particles (10 μg/cm^2) on 16HBE cells, the latter weakly induced the release of GM–CSF and activated nuclear factor-κB (Bonvallot *et al*., 2001).

To investigate whether reduced clearance from the lung after exposure to ultrafine particles may be due to impaired phagocytosis by alveolar macrophages, an in-vitro study was conducted with the macrophage cell line J774.2 MΦ. The cells were exposed for 8 hours to fine titanium dioxide (mean diameter, 250 nm; 6.6 m^2/g), ultrafine titanium dioxide (mean diameter, 29 nm; 49.8 m^2/g), carbon black (Huber 990; mean diameter, 260.3 nm; 7.9 m^2/g) or ultrafine carbon black (Printex 90; mean diameter, 14.3 nm; 253.9 m^2/g). The particles had no cytotoxic effects. The ability of the macrophages to phagocytose 2-μm latex beads was significantly reduced ($P < 0.001$) after exposure to 0.39 μg/mm^2 ultrafine carbon black and 0.78 μg/mm^2 of all particle types compared with the control. Furthermore, ultrafine carbon black induced a significant ($P < 0.001$) reduction in macrophage phagocytosis at a lower dose than fine carbon black (0.39 and 0.78 μg/mm^2, respectively). At all doses, exposure to ultrafine carbon black resulted in a

larger number ($P < 0.001$) of non-phagocytic macrophages compared with the other particle types. The culture medium collected after exposure of macrophages to particles had no significant effect on the phagocytic ability of naive macrophages, which suggests that cell-to-cell contact rather than a soluble factor was responsible for the defective phagocytosis. The authors concluded that slowed clearance of particles, especially ultrafine particles, can in part be attributed to a particle-mediated impairment of macrophage phagocytosis (Renwick *et al*., 2001; see also the in-vivo study by Renwick *et al*., 2004, discussed above).

Because ultrafine particles and transition metals have been postulated to be important determinants of the toxicity and potential adverse health effects of particulate air pollution, the interactions between transition metal salts and fine and ultrafine carbon black particles were studied. In all experimental systems used, the ultrafine particles were more reactive than the larger-sized particles. Incubation of ultrafine carbon black (Printex 90; diameter, 14 nm; 253.9 m^2/g) with the reactive oxygen species-sensitive probe dichlorofluorescin diacetate in a cell-free system generated significantly more reactive oxygen species than the larger-sized carbon black particles (Huber 990; 260 nm; 7.9 m^2/g). Addition of cupric sulfate, ferrous sulfate or ferric chloride further increased the generation of reactive oxygen species induced by ultrafine carbon black. In Mono Mac 6 macrophages (a human monocytic cell line), the 14-nm carbon black again produced more reactive oxygen species than the 260-nm particles, but iron salts had no additive effect. Ultrafine carbon black decreased the cellular content of glutathione (GSH) and adenosine triphosphate (ATP) in the murine macrophage cell line J774. Further reductions in GSH and ATP were seen after the addition of iron salts but only at the highest concentration tested (500 μM). A concentration-dependent increase in the production of TNFα was also observed in J774 cells after exposure to ultrafine carbon black, but this effect was not further enhanced by the addition of iron salts even at the highest concentration tested (500 μm). In the rat lung, ultrafine carbon black (125 μg) induced a significant influx of neutrophils in the BAL fluid. This inflammatory effect was enhanced by the addition of ferric chloride (100 μM), which was inactive alone. The authors concluded that ultrafine particles and metal salts interact by chemical potentiation in a cell-free system to generate reactive oxygen species. This potentiation was not observed in the presence of macrophages, probably because the iron is sequestered or chelated by the cells. In the lung, ultrafine particles and iron salts interacted synergistically in generating inflammation (Wilson *et al*., 2002).

The capacity of fine carbon black (Huber 990; diameter, 260 nm; 7.9 m^2/g) to activate serum factors that stimulate the migration of murine alveolar macrophages was compared with that of ultrafine carbon black (Printex 90; diameter, 14 nm; 254 m^2/g). Incubation of fetal bovine serum with 5 and 10 mg/mL ultrafine carbon black caused a 1.4- and 1.8-fold increase, respectively, in migration of macrophages compared with untreated serum. These effects were partially inhibited by further incubation with antioxidants (Trolox or Nacystelin). An equivalent mass of fine carbon black (10 mg/mL) did not show chemotactic activity. On an equal mass basis, ultrafine carbon black particles activated

serum factors, possibly C5a-like proteins, to a greater extent than fine carbon black particles (Barlow *et al*., 2005).

The mouse monocyte/macrophage cell line RAW264.7 was used to determine the adverse effects of exposure *in vitro* to 30 and 120 μg/mL size-fractionated urban air particles (particulate matter (PM) 2.5–10; $PM_{2.5}$) collected in the city of Rome and carbon black (Huber NG90; diameter, 200–250 nm). Urban air particles induced a significant release of arachidonic acid after a 5-hour exposure at both concentrations, while carbon black was effective only at 120 μg/mL. After 5 hours, the 120-μg/mL concentration of the two PM fractions stimulated the production of TNFα about 10-fold more strongly than carbon black particles, but the stimulation diminished after 24 hours. In contrast, carbon black-stimulated TNFα production did not show such a decrease. Production of IL-6 was enhanced by incubation with urban air particles but not with carbon black. Carbon black was consistently less effective than the urban particles (Pozzi *et al*., 2003).

Chin *et al*. (1998) evaluated the role of adsorbed mutagens, such as benzo[*a*]pyrene, on carbon black particles in cellular response and signal transduction. A cultured macrophage cell line (RAW264.7) was exposed to carbon black (N339; diameter, 0.1 μm) and benzo[*a*]pyrene-adsorbed carbon black (2 μg/mL benzo[*a*]pyrene) for up to 24 hours. The benzo[*a*]pyrene-adsorbed carbon induced time-dependent expression and release of TNFα and apoptosis in RAW cells, which were inhibited by a TNFα-neutralizing antibody. Neither carbon black nor benzo[*a*]pyrene alone induced these effects. TNFα activates mitrogen-activated protein kinase (MAPK) activity and the extracellular signal-regulated kinases p42/44 in a time-dependent manner, and treatment of RAW264.7 cells with the MAPK inhibitor PD-098059 inhibited the apoptosis and TNFα secretion induced by benzo[*a*]pyrene-adsorbed carbon black. The results indicated that adsorbed mutagens on carbonaceous particles may play a role in the induction of apoptosis and inflammatory responses, such as the release of cytokines like TNFα.

Ultrafine particles including carbon black (Printex 90, diameter, 12 nm; 300 m^2/g), elemental carbon (diameter, 90 nm; 600 m^2/g) and diesel exhaust particles (diameter, 120 nm; 108 m^2/g; 10–320 μg/mL/10^6 cells) caused a variety of cytoskeletal dysfunctions including impaired phagocytosis (approximately 50% of controls), inhibited cell proliferation and decreased cell viability in primary alveolar macrophages from dogs and a mouse alveolar macrophage cell line (J774A.1) within 24 hours of treatment with a dose of 320 μg/mL/10^6 cells (Möller *et al*., 2002).

4.3   Reproductive and developmental effects

4.3.1   *Humans*

No data were available to the Working Group.

4.3.2   Animals

In a study designed to evaluate the effects of subacute exposure to inhaled benzo[*a*]pyrene (adsorbed on a carbon black carrier) on testicular steroidogenesis and epididymal function in Fischer 344 rats, one of the control groups was exposed to carbon black alone (Elftex 12; 4 hours daily for 10 days). Blood and sperm samples were collected immediately after the last exposure on day 10, and 24, 48 and 72 hours later. There were no differences in progressive sperm motility or serum testosterone concentration in the rats exposed to carbon black only compared with untreated controls. [The study showed that subacute exposure to inhaled benzo[*a*]pyrene adsorbed on carbon black affects testosterone levels and epididymal function] (Inyang *et al*., 2003).

4.4   Genetic and related effects (for details and references, see also Table 4.3)

4.4.1   *Humans*

No data were available to the Working Group.

4.4.2   *Experimental systems*

Carbon black has been found to be negative in most assays for mutagenicity (IARC, 1996). In rats exposed by inhalation to carbon black for 12 weeks, the hypoxanthine(guanine) phosporibosyltransferase gene *(Hprt)* mutant frequency was elevated in type II cells; however, carbon black did not induce a significant increase in DNA adducts in the peripheral lung tissue of rats after two years of inhalation exposure. In another study, exposure of rats by inhalation to carbon black increased DNA adduct levels in type II cells, while K-*ras* mutations were found in one of 18 neoplasms analysed from carbon black-exposed rats. No exposure-related *p53* mutation was found.

Most in-vitro mutagenicity studies of carbon black have given negative results, including several Ames tests, mouse lymphoma assays and mouse embryo morphological cell transformation assays (IARC, 1996). Carcinogenicity studies in rats *in vivo* have led to the proposal that secondary genotoxicity of carbon black is based on an overloading mechanism that leads to the generation of reactive oxygen species from infiltrated inflammatory cells, the oxidation of DNA bases and DNA strand breaks or lipid peroxidation, the secretion of inflammatory mediators that have been independently implicated in secondary genotoxic and proliferating events that lead to tumour formation from poorly soluble dust (Driscoll *et al*., 1997; Gallagher *et al*., 2003; Gilmour *et al*., 2004; Elder *et al*., 2005). The release of inflammatory mediators or factors, such as leukotrienes, reactive oxygen species, cytokines (TNFα, IL-1, IL-8), fibronectin and transforming growth factor β, is already known to be involved in the damage of local tissue and remodelling (Borm & Driscoll, 1996). The overloading that leads to the secondary genotoxic mechanism, which involves persistent lung inflammation and injury, is dependent on the species of animal, surface coating and composition, as seen with diesel

Table 4.3. Genetic and related effects of carbon blacks or their formulations

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA strand breaks, isolated ΦX174 replicative form supercoiled plasmid *in vitro*	+[c]	NT	20	Dick *et al.* (2003)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	−[d]	−[d]	3750	Kirwin *et al.* (1981)
Salmonella typhimurium TA100, TA98, reverse mutation	+[e]	+[e]	NR	Agurell & Löfroth (1983)
Salmonella typhimurium TA100, reverse mutation	−[f]	−[f]	50 mg/plate	Venier *et al.* (1987)
Salmonella typhimurium TA98, reverse mutation	−[g]	NT	250	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	(+)[h]	NT	500	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	+[i]	NT	5.0	Rosenkranz *et al.* (1980)
Salmonella typhimurium TA98, reverse mutation	(+)[f]	+[f]	5.0 mg/plate	Venier *et al.* (1987)
Salmonella typhimurium nitroreductase deficient strains TA98NR, TA98/1,8DNP, reverse mutation	+[e]	NT	NR	Agurell & Löfroth (1983)
Drosophila melanogaster, somatic mutation (mosaics), sex-linked recessive mutation, dominant lethal test, aneuploidy (sex-chromosome loss)	−[d]		10 000 larval feeding	Kirwin *et al.* (1981)
DNA strand breaks, Comet assay, Chinese hamster V79 cells *in vitro*	−[k]		137.9 µg/cm^2, 3 h	Zhong *et al.* (1997)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	−[d]	−[d]	40 000	Kirwin *et al.* (1981)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	−[d]	−[d]	1000	Kirwin *et al.* (1981)
Micronucleus formation, M3E3/C3 hamster epithelial cells *in vitro*	+[l]	NT	1	Riebe-Imre *et al.* (1994)
Anchorage independent growth, M3E3/C3 hamster lung epithelial cells *in vitro* (undifferentiated and differentiated small mucus granule cell stage)	+[l]	NT	100	Riebe-Imre *et al.* (1994)
Cell transformation, C3H/10T½ mouse fibroblasts *in vitro*	−[d]	NT	16 000	Kirwin *et al.* (1981)

Table 4.3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA adduct formation, ^{32}P-postlabelling (PAH–DNA adducts), A549 human lung epithelial cells *in vitro*	−[m]		100 µg/cm^2	Borm *et al.* (2005)
DNA strand breaks, Comet assay, human A549 and monocytic THP-1 cells *in vitro*	?[j]		1.6	Don Porto Carero *et al.* (2001)
DNA strand breaks, Comet assay, human embryonic lung HEL 299 cells in vitro	−[k]		137.9 µg/cm^2, 3 h	Zhong *et al.* (1997)
DNA adduct formation, ^{32}P-postlabelling, (PAH–DNA adduct) Fischer 344 rats *in vivo*	−[m]		50 mg/m^3, inh, 13 wks	Borm *et al.* (2005)
DNA adduct formation, ^{32}P-postlabelling in female Wistar rat lung *in vivo*	−[n]		11.3 mg/m^3, inh, 18 h/d × 5 d/wk × 2 yr,	Gallagher *et al.* (1994)
DNA adduct formation, (8-oxo-dG), Fischer 334 rat lung *in vivo*	+[o]		50 mg/m^3, 6 h/d × 5 d/wk × 13 wk; 7 mg/m^3, 44 wk recovery	Gallagher *et al.* (2003)
Tp53, K-*Ras* mutation in pulmonary carcinomas in Fischer 344/N rats *in vivo*	−[p]		6.5 mg/m^3, 16 h/d × 5 d/wk × 24 mo	Swafford *et al.* (1995); Belinsky et al. (1997)
Gene mutation, *Hprt* locus, type II alveolar cells isolated from rats treated *in vivo*	+[q]		7.1 mg/m^3, inh, 6 h/d × 5 d/wk × 13 wk	Driscoll *et al.* (1996)

Table 4.3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Gene mutation, *Hprt* locus, rat alveolar epithelial RLE-6TN cells exposed to BAL fluid from rats exposed *in vivo*	+[r]		100 mg/kg bw, it, 15 mo after	Driscoll *et al.* (1997)
Binding to DNA (DNA adduct) (^{32}P-postlabelling) in Fischer 344/N rat alveolar type II cells *in vivo*	+[p]		6.2 mg/m^3, inh, 16 h/d × 5 d/wk × 12 wk	Bond *et al.* (1990)

[a] +, positive; (+), weak positive; –, negative; ? inconclusive;

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw; d, day; inh, inhalation; it, intratracheal; mo, month;NR, not reported; NT, not tested; wk, week; yr, year; 8-oxo-dG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; 1,8 DNP, 1,8 dinitropyrene

[c] Ultrafine carbon black; diameter, 14 nm; surface area, 253.9/m^2/g

[d] Rubber-grade furnace black N339; surface area, 100 m^2/g; 48-h toluene extractables 0.15%; particles suspended in dimethyl sulfoxide (DMSO) (Ames test + sister chromatid exchange assay), acetone (cell transformation test) or culture media (mouse lymphoma test)

[e] Carbon blacks from various manufacturers (20 samples); Soxhlet extraction of 1-g samples with 200 mL benzene for 16 h and solvent exchange into DMSO

[f] Carbon black used for refining tanned skins (7 samples); (a) sonication of 2 g samples in 40 mL benzene for 0.5 h; (b) Soxhlet extraction of 4-g samples with 50 mL toluene for 48 h; solvent exchange into DMSO (1 g extract/mL)

[g] Black Pearls L (furnace black, manufacture of which involves a nitration-oxidation step); suspension in DMSO at 5 mg/mL for 5 h before testing

[h] Raven 5750 (furnace black, oxidative after-treated); soxhlet extraction of 10-g samples with toluene for 48 h; low-temperature concentration and solvent exchange into 1 mL DMSO

[i] Black Pearls L (furnace black, manufacture of which involves a nitration-oxidation step); Soxhlet extraction of 10 g samples with toluene for 48 h; low-temperature concentration and solvent exchange into 1 mL DMSO

[j] Vulcan M, furnace black, carbon black mean diameter, 100 nm, 8 mg/5 mL of RPMI medium

[k] Cabot NJ, 37 nm, 8 mg/mL MEM

[l] Carbon black [not otherwise characterised]; carbon black suspended in the culture medium containing undifferentiated cells for 72 h

[m] Printex-90, 300 m^2/g, Sterling V, 30–40 m^2/g; N330, 70–90 m^2/g; Lampblack 101, 20 m^2/g; suspended in Hank's balanced salt solution *in vitro*, whole-body exposure *in vivo*

[n] Printex-90 (furnace black); MMAD, 0.65 m; surface area, 270 m^2/g; carbon black in air at 2 yr mean of 11.3 mg/m^3; whole-body exposure

[o] Printex-90, 16 nm, surface area 300 m^2/g; whole-body exposure

[p] Elftex-12 (furnace black); 2 µm MMAD (large mode); 0.1 µm MMDD (small mode); surface area, 43 m^2/g; whole-body exposure

[q] Monarch 880; 16 nm; surface area, 220 m^2/g; MMAD 880 nm; whole-body exposure

[r] Monarch 900; 15 nm; surface area, 230 m^2/g, intratracheal instilltion

exhaust particles and carbon black (a surrogate for carbonaceous particles), particle size and shape, and surface area (Schins, 2002; Gallagher *et al*., 2003; Gilmour *et al*., 2004).

Male Fischer rats were exposed for 6 hours per day on 5 days per week for up to 13 weeks to 1.1, 7.1 and 52.8 mg/m^3 carbon black (Monarch 880; diameter, 16 nm; surface area, 220 m^2/g). Mutagenesis in alveolar epithelial cells was assessed after 6.5 and 13 weeks of exposure and after 3 and 8 months of recovery. *Hprt* mutation frequency was significantly increased in alveolar epithelial cells after 13 weeks of exposure to 7.1 and 52.8 mg/m^3 carbon black and after 3 and 8 months of recovery in high-dose rats. No increase in *Hprt* mutation frequency was seen in the low-dose group. The induction of mutation in alveolar epithelial cells occurred after carbon black exposures that resulted in significant inflammation and epithelial hyperplasia (see Section 4.2.2) (Driscoll *et al*., 1996).

Driscoll *et al*. (1997) investigated lung adenomas and carcinomas in female Fischer rats exposed by intratracheal instillation to poorly soluble particles (10 or 100 mg/kg bw α-quartz or carbon black; Monarch 900; diameter, 15 nm; surface area, 230 m^2/g) and the relationship between exposure to particles, inflammation and mutagenesis in alveolar type II cells. After 15 months of exposure, BAL cells were examined histopathologically. Neutrophilic inflammation was detected in the rats exposed to 10 and 100 mg/kg bw carbon black and epithelial hyperplasia was observed in the rats exposed to 100 mg/kg bw carbon black. The frequency of *Hprt* mutations was higher in alveolar epithelial type II cells of rats exposed to 100 mg/kg bw carbon black. In-vitro exposure of rat lung epithelial RLE-6TN cells to BAL cells from rats treated with 100 mg/kg bw carbon black or with 10 or 100 mg/kg bw α-quartz also increased the frequency of *Hprt* mutants, but addition of catalase to BAL cell:RLE-6TN co-cultures inhibited this increase (the effect of catalase was tested only with BAL cells from rats treated with α-quartz). The authors concluded that inhibition of the BAL cell-induced mutations by catalase implies that cell-derived oxidants play a role in this response, whereas the ability of particle-elicited macrophages and neutrophils to exert a mutagenic effect on epithelial cells *in vitro* supports a potential role for these inflammatory cells in the mutagenic effects of particle exposure *in vivo*.

Gallagher *et al*. (2003) tested the hypothesis that chronic inflammation and cell proliferation play a role in the development of tumours after long-term high-dose particle contact with lung epithelial cells. Female Fischer 344 rats were exposed to 1, 7 and 50 mg/m^3 Printex 90 carbon black (diameter, 16 nm; surface area, 300 m^2/g) and 50 mg/m^3 Sterling V carbon black (diameter, 70 nm; surface area, 37 m^2/g) for 6 hours per day on 5 days per week for 13 weeks. A significant increase in the induction 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) was observed in the lung following the 13-week exposure to 50 mg/m^3 Printex 90 and a 44-week recovery period. However, no increase in 8-oxo-dG was observed with Sterling V carbon black after 13 weeks of exposure or during the 44-week recovery period. Since neither Sterling V (50 mg/m^3) nor Printex 90 (7 mg/m^3) induced a significant increase in 8-oxo-dG in the lung at the end of the 13-week exposure, the retained large particle mass was not correlated with adverse

effects, whereas the particle surface area was a better dose parameter for the induction of 8-oxo-dG. The authors suggested that prolonged high-dose exposure to carbon black can promote oxidative DNA damage, which is consistent with the hypothesis that inflammatory cell-derived oxidants may play a role in the pathogenesis of rat lung tumours following long-term high-dose exposure to carbon black.

Carbon black did not induce a significant increase in DNA adducts (detected as a diagonal radioactive zone to identify nitrated amine or arylamine adducts) in the peripheral lung tissue of rats after 2 years (Gallagher *et al*., 1994) or 12–13 weeks of inhalation exposure (Bond *et al*., 1990; Borm *et al*., 2005). In other inhalation studies, rats exposed to carbon black for 3 months had a significant but not dose-related increase in DNA adducts in alveolar epithelial cells (Mauderly *et al*., 1994). K-*ras* and *Tp53* mutations, which are markers of the early stages of squamous-cell carcinoma in humans, may not be related to exposure to carbon black (Swafford *et al*., 1995; Belinsky *et al*., 1997).

Carbon black that is used as a surrogate for diesel exhaust particle carbon core includes significant amounts of adsorbed organic materials that have been identified as mutagenic. Carbon black and diesel exhaust particles have already been tested in various experimental systems to compare the contribution of the chemicals adsorbed onto carbon black to mutagenesis and immunomodulation. Absorbed chemicals, such as PAHs, are very tightly bound to carbon black; however, PAHs are released from organic extracts of low-surface area particles with a high PAH content (Borm *et al*., 2005). The contrasting cellular response to exposure to diesel exhaust particles and carbon black may be due to the presence of adsorbed organic components in the former. Exposure of rats to carbon black increases TNFα production of the alveolar macrophages, while exposure to diesel exhaust particles does not, which indicates that adsorbed organic compounds, including PAHs, play a role in host susceptibility to pulmonary infection (Yang *et al*., 1999).

Additional genotoxicity assays, including a Comet assay (single-cell gel electrophoresis), gave negative results for carbon black in human embryonic lung Hel 299 fibroblasts and Chinese hamster V79 cells and positive results in T-cell THP-1 and human lung A541 cells but only at a high dose (1600 ng/mL) (Zhong *et al*., 1997; Don Porto Carero *et al*., 2001). DNA adducts were observed only for one of four carbon black samples in lung epithelial cells *in vitro* (Borm *et al*., 2005).

Timblin *et al*. (2002) studied proto-oncogene expression, proliferation and apoptosis in murine alveolar epithelial cells after exposure to ultrafine carbon black (Monarch 880) at a concentration of 10 μg/cm^2 for 24 and 48 hours. A significant increase in the number of cells in the S phase of the cell cycle was observed, which suggested early injury and subsequent unscheduled DNA synthesis that may represent compensatory cell proliferation. After 24 and 48 hours, a significant decrease in the percentage of cells in the G_2/M and an elevation of that in the $subG_0/G_1$ followed by a decrease in the number of cells in the G_0/G_1 were observed, which indicated apoptosis. Ribonuclease protection assays demonstrated that cells exposed to ultrafine carbon black for 8 hours had increased mRNA levels of proto-oncogenes *fos* and *jun* and apoptosis associated genes *fas* and

caspase 8. In contrast, cells exposed to the fine carbon black (Monarch 120) had a significant increase in only *fra*-1 mRNA levels, demonstrating that ultrafine carbon black stimulated changes in the expression of genes linked to both proliferative and apoptic pathways.

The effects of fine and ultrafine carbon black on rat BAL macrophages and human blood monocytes were investigated with regard to the roles of calcium and reactive oxygen species. Ultrafine carbon black (Printex 90; mean diameter, 14 nm) but not fine carbon black (Huber 900; mean diameter, 260 nm) was found to increase the resting cytosolic Ca^{2+} concentration in these cells when tested at equal mass (200 μg/mL). The calcium channel blocker, verapamil, reduced intracellular calcium concentration and activation of transcription factor AP-1 in rat alveolar macrophages after stimulation with ultrafine carbon black. A calcium antagonist and an antioxidant (Trolox and Nacystelin) also reduced ultrafine carbon black-stimulated NF-κB activation in human monocytes, as well as ultrafine carbon black-stimulated TNFα protein release in rat alveolar macrophages and human monocytes. The authors suggested that ultrafine particles may exert pro-inflammatory effects by modulating intracellular calcium concentrations, activation of transcription factors and cytokine production through a reactive oxygen species-mediated mechanism (Brown *et al*., 2004).

To study the effects of ultrafine particles on airway epithelial cell proliferation, normal human bronchial epithelial cells were exposed to 6.1–30.7 μg/cm^2 ultrafine (diameter, 11.2 nm; 457 m^2/g) and fine (diameter, 250 nm; 7.8 m^2/g) carbon black. Ultrafine carbon black elicited proliferation in a time- and dose-dependent manner and activated the extracellular signal-regulated kinase signalling pathway in an antioxidant- and epidermal growth factor receptor-dependent manner. Accordingly, the authors suggested that ultrafine carbon black causes oxidative stress-mediated proliferation of airway epithelium (Tamaoki *et al*., 2004).

4.5   Comparison of toxicokinetics and toxicodynamics of inhaled poorly soluble particles in animals and humans

Several studies have shown that rats, but not mice or hamsters, develop excess incidences of lung cancer after chronic inhalation of 'overloading' doses of poorly soluble particles. Several studies have discussed this phenomenon and the challenges it poses for the extrapolation of chronic effects in rats to the human situation (Morrow, 1994; Levy, 1995; Oberdörster, 1995; Watson & Valberg, 1996; ILSI Risk Science Institute Workshop Participants, 2000; Miller, 2000; Oberdörster *et al*., 2002; Rausch *et al*., 2004; Hext *et al*., 2005).

To evaluate the appropriateness of the rat as an experimental model to assess the carcinogenic hazard of poorly soluble particles in the lungs of humans, it is necessary to assess the scientific evidence that allows for comparisons among species of exposure, dose, response and mode of action. A conceptual framework is presented in Fig. 4.2.

CARBON BLACK   167

Figure 4.2. Conceptual framework of carcinogenesis induced by poorly soluble particles in rats
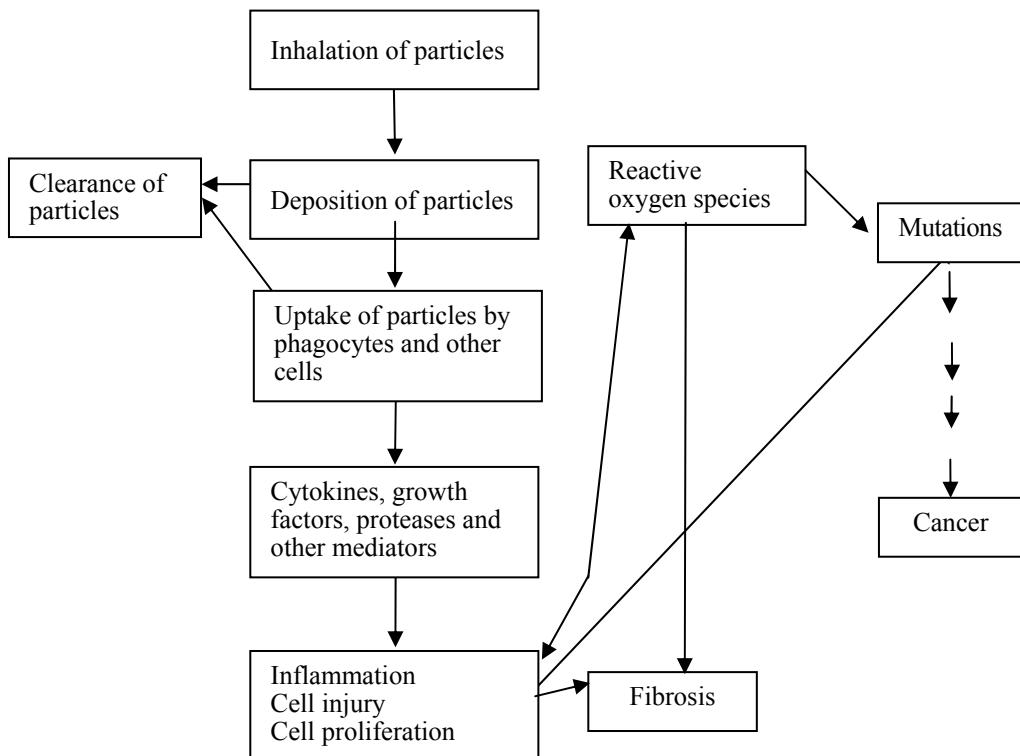
The scheme represents the sequence of events and modes of action that are considered to be involved in the formation of tumours that are observed in the lungs of rats after high exposure to poorly soluble particles (see text for further details)

4.5.1   *Exposure–dose relationship*

Inhaled particles may present a hazard when they are deposited in sufficient quantities (dose) and interact with cells or tissues at responsive target sites along the respiratory tract. The relationship between exposure to particles and inhaled dose is described by the kinetics of particle deposition and clearance, and may be influenced by the retained particle dose (see Section 4.1.1.*c*). The kinetic differences in exposure–dose relationships of inhaled particles in humans and rats, including the kinetics of overloading, can be described quantitatively using lung dosimetry models (see Section 4.1.3). Inhaled and deposited particles are cleared from the normal lungs of healthy rats more rapidly than from those of humans. However, at high lung burdens, normal clearance from the rat lung can be impaired and the lung can be inundated to such a degree that, in time, clearance

effectively ceases. This phenomenon (which is termed 'overload') is observed with poorly soluble particles that are generally considered to have low toxicity (Morrow, 1988). Overload was originally described in terms of the particle dose as either a mass or volume (to take into account differences in particle density). However, ultrafine particles have been observed to cause impaired clearance at much lower mass doses than fine particles (Lee *et al*., 1985a; Heinrich *et al*., 1995; Bermudez *et al*., 2002, 2004). Dose of particle surface area was shown to be a better predictor of key indicators of rat lung overload (i.e. increased particle retention and neutrophilic inflammation) in a study that used two fine particles with different specific surface areas (titanium dioxide and barium sulfate) and compared these results with those of ultrafine titanium dioxide from another study (Oberdörster *et al*., 1994a; Tran *et al*., 2000).

Much more is known about overload in rats than in humans. Inundated or impaired alveolar macrophage-mediated clearance in rats has been postulated as a pivotal factor in the development of lung overload (Morrow, 1988). The same factors that interfere with clearance in rats may contribute to accumulation of particle mass dose in humans. Although no kinetic data are available to determine whether overload occurs in humans by processes similar to those described in rats, reduced lung clearance and retained mass lung burdens comparable with those that cause overloading in rats have been observed in coal miners (Freedman & Robinson, 1988; Freedman *et al*., 1988). Historically, the average lung burdens of particle mass in coal miners (approximately 14 g per whole lung) (Stöber *et al*., 1965; Kuempel, 2000; Tran & Buchanan, 2000) have exceeded the doses associated with overload and substantial impairment of clearance in rats ($\approx$10 mg/lung) (Muhle *et al*., 1990a).

At sufficient concentrations and durations of exposure to inhaled fine particles, rats may accumulate greater masses of particles than the lung burdens seen in most workers. Conversely, for ultrafine particles, the retained mass doses associated with impaired clearance in rodents are similar to lung burdens that could occur in workers. For any experimental model that is used for hazard assessment in humans or to evaluate dose–response relationships, it is important to evaluate doses in experimental animals that are comparable with those that may occur in humans.

Lung clearance can also become impaired in humans and experimental animals for reasons other than overload (Morrow, 1988). For example, in humans, toxic gases and particles have been shown to impair clearance by affecting normal cilia function, mucous rehology and phagocytosis. Ultrafine particles may be cleared less effectively than larger-sized particles due to impaired phagocytosis (Renwick *et al*., 2001, 2004; Geiser *et al*., 2005).

Impaired clearance and overload are not unique to rats, but can also occur in other species although to different degrees (Bermudez *et al*., 2002, 2004; Elder *et al*., 2005). In contrast, overload has not been observed in hamsters at concentrations at which it readily appears in rats and mice, and clearance in hamsters seems to be affected to a lesser degree or recovers quickly. How human lung clearance would behave under similar circumstances is unclear but, by analogy to coal workers, chronic impairment of clearance

occurs and often persists long after exposure ceases (Freedman & Robinson, 1988; Freedman *et al*., 1988).

Rats chronically exposed to sufficiently high concentrations of poorly soluble particles experience a steady reduction in alveolar clearance rates and an accumulation of intralumenal and interstitial particles (Ferin *et al*., 1992; Oberdörster *et al*., 1994a,b; Warheit *et al*., 1997; Bermudez *et al*., 2002, 2004). In rodents, ultrafine particles translocate to the interstitium to a greater extent than fine particles (Ferin *et al*., 1992; Oberdörster *et al*., 1992, 1996; Geiser *et al*., 2005). In studies that compared the pattern of particle retention in the lungs of rats, monkeys and humans exposed to coal dust and/or diesel exhaust, a higher volume percentage of dust was observed in the alveolar lumen of rats than in the interstitium of monkeys and humans (Nikula *et al*. 1997a,b, 2001); however, no data were available to compare the actual retained doses in the specific lung regions of each species. The biological significance of the interstitial/lumenal distribution in the development of overload and the consequent toxic sequel is not clear, either within a given species or among species.

4.5.2   *Dose–response relationships*

With continued inhalation of sufficiently high concentrations of particles, rats that achieve overload may develop pulmonary fibrosis and lung tumours (Lee *et al*., 1985a,b, 1986; Warheit *et al*., 1997). Oberdörster (1996, 2002) proposed that the effects of high doses observed in rats may be associated with two thresholds: (1) a pulmonary dose that results in reduced macrophage-mediated clearance which leads to shut-down and overload and (2) a higher dose associated with overload at which normal antioxidant defences within the lung are overwhelmed and pulmonary tumours may initiate and develop.

In contrast to fine particles, much lower concentrations of ultrafine particles (e.g. 2.5, 6.5 or 11.5 mg/m^3 carbon black and ~10 mg/m^3 ultrafine titanium dioxide) were associated with impaired clearance, persistent inflammation and malignant lung tumours in chronic inhalation studies in rats (Heinrich *et al*., 1995; Nikula *et al*., 1995).

(a)   Mechanistic considerations (overall mode of action)

A cascade of events that was proposed to describe the biological process that starts with some particle deposition at critical target cells or tissues within the rat lung and results in rat lung tumours includes: sustained inflammation, production of reactive oxygen species, depletion of antioxidants and/or impairment of other defence mechanisms, cell proliferation and gene mutations. These individual steps comprise an overall mode of action that can be used to compare responses of rats with those of other species including humans (see Fig. 4.2). The dose metric that best describes the dose–response relationship for poorly soluble particles in the rat lung has been examined in various studies (Driscoll *et al*., 1996; Pott & Roller, 2005; Morfeld *et al*., 2006). The

surface area, volume and size of particles have all been shown to be related to the tumour response in rats.

At particle lung burdens that are associated with impaired clearance in rats (e.g. beginning at a mass dose of ~0.5 mg/lung and completely overloaded at ~10 mg/lung for fine particles of unit density; Muhle *et al*., 1990a), a sustained and widespread cellular inflammatory response occurs. The cell population is dominated by activated and probably (under these conditions) persistent polymorphonuclear neutrophils and secretes a collection of mediators (reactive oxygen species, pro-/anti-inflammatory cytokines, proteases, cytotoxins, fibrogenic and other growth factors) that act through the pulmonary milieu on surrounding cells or tissues and surrounding structures (Castranova, 1998, 2000; Knaapen *et al*., 2004). The degree of sustained inflammation experienced by rodents (most notably rats) at high lung burdens has not been observed in humans. However, humans may experience sustained inflammation in certain disease states. One such human condition (which may be particle-stimulated—e.g. by silica—or may be cytogenic) is late-stage, interstitial pulmonary fibrosis (Daniels & Jett, 2005). Patients with interstitial pulmonary fibrosis and chronic inflammation have been reported to develop a higher incidence of lung tumours, frequently in the most inflamed areas. In addition, chronic inflammation has been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom (1991) found a statistically significant increase in the percentage of polymorphonuclear neutrophils in the BAL fluid of workers with respiratory impairment who had been exposed to asbestos, coal, or silica (4.5% in cases versus 1.5% in controls). Elevated levels of polymorphonuclear neutrophils have been observed in the BAL fluid of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3% in controls) (Vallyathan *et al*., 2000) and in patients with acute silicosis (a 10-fold increase over controls) (Goodman *et al*., 1992; Lapp & Castranova 1993). An elevated incidence of lung cancer has been observed in some workers exposed to poorly soluble particles including crystalline silica (Rice *et al*., 2001; Attfield & Costello, 2004) and diesel exhaust particles (Stayner *et al*., 1998), although these materials may have greater inherent toxicity than other poorly soluble particles such as titanium dioxide, carbon black and talc.

The precise role of chronic inflammation in the development of cancer is uncertain, but there is considerable evidence that chronic inflammation may have a multifaceted role in this process. Activated cells in the lung are known to release various reactive intermediates, most notably those derived from oxygen. Sustained excess of oxidant activity is known to deplete antioxidant defences gradually. These defence mechanisms in the lungs of humans and rats clearly differ, in that humans are overall relatively deficient in some of them (Slade *et al*., 1985). Reactive oxygen species within cells may damage DNA directly and potentially induce mutations. Moreover, cell damage and promitotic stimuli initiated by reactive oxygen species promote cell turnover and proliferation, events that may enhance the risk for DNA replication error and/or expand a mutated or transformed cell to initiate a tumour.

The mechanism that involves inflammation and oxidative stress which lead to tumour formation is considered to be a secondary genotoxic mechanism, in contrast to a primary genotoxic mechanism in which the agent interacts directly with DNA (Knaapen *et al*., 2004).

(b)   Interspecies extrapolation

There remains uncertainty with regard to identifying in detail the cascade of events that lead to rat lung cancer following inhalation of poorly soluble particles that include talc, carbon black and titanium dioxide. However, as shown in Fig. 4.2, several important steps can be identified that are supported by a substantial rodent database. An important question that needs to be addressed is the extent to which the steps outlined in Fig. 4.2 for rat lung cancer are also operative in other animal species including humans. The majority of animal studies that have evaluated the effects of poorly soluble particles on the respiratory tract have been conducted in rats; species differences such as particle inhalability, breathing conditions, respiratory tract structure and pulmonary defences need to be considered when toxicological findings from rodents are extrapolated to humans (Brown *et al*., 2005). Exposure to airborne particles would generally need to be higher in rats to result in equivalent particle doses in the human lung (Brown *et al*., 2005).

All animals species used routinely in particle toxicology and humans are susceptible to impairment of clearance of poorly soluble particles from the lungs. Impaired clearance is probably one of the first steps necessary to initiate a sequence of events that may lead to lung cancer in rats exposed to poorly soluble particles (see Fig. 4.2). However, different animal species exhibit differences in particle-induced impairment of clearance, which can result in different lung burdens (expressed as mass or surface area) following exposures to the same particle concentrations (Elder *et al*., 2005).

Similarly, pulmonary inflammation has been reported to be a consequence of exposures to poorly soluble particles in both experimental animals and humans (Driscoll *et al*., 1996; Elder *et al*., 2005; Shwe *et al*., 2005; Rom, 1991; Vallyathan *et al*., 2000). The pathophysiology of particle-induced fibrosis in humans and fibrosis and lung cancer in rats from lung overload—with lung burden being expressed as mass, volume and/or surface area for fine and ultrafine particles—involves chronic inflammation, hyperplasia and cell proliferation, altered collagen deposition and architecture.

Rats and mice, in contrast to hamsters, exhibit sustained inflammation associated with particle lung burden, but lung tumours induced by poorly soluble particles have only been observed in rats. It has been shown that rats are uniquely susceptible to poorly soluble particle-induced lung cancer relative to mice and hamsters. While some of the steps indicated in Fig. 4.2 have been demonstrated in humans exposed to poorly soluble particles, it is not known to what extent humans are susceptible to particle-induced lung cancers associated with titanium dioxide, carbon black or talc.

4.5.3 *Alternative mechanisms*

Studies of poorly soluble particles in rodents provide evidence to support the hypothesis that one mode of action involves chronic inflammation, epithelial proliferation and the generation of reactive oxygen species that lead to mutagenic event(s) proximate to cancer. Alternative mechanisms to these could be involved, although the data to support them are limited. For example, it has been shown that particles such as carbon black, titanium dioxide and talc can translocate, once deposited on the lung surface, into the lung epithelial cells which are considered to be progenitor cells for some types of tumour that are associated with the inhalation of poorly soluble particles. Poorly soluble particles may interfere with the cytoskeleton during cell division, which may lead to aneuploidy and elicit genotoxicity.

4.6   **References**

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CARBON BLACK 173

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CARBON BLACK   183

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IARC MONOGRAPHS VOLUME 93

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5. Summary of Data Reported

5.1   Exposure data

Carbon black is a generic term for a particulate form of elemental carbon manufactured by the vapour-phase pyrolysis and partial combustion of hydrocarbons. Carbon blacks are categorized, on the basis of different production processes by which they are made, as acetylene black, channel black, furnace black, lampblack or thermal black. Acetylene, furnace and thermal blacks have been produced since the early twentieth century. Over 95% of all carbon black produced today is furnace black. Worldwide production capacity of carbon black in 2005 was approximately 10 million tonnes.

Carbon blacks are characterized by the size distribution of the primary particles and the degree of their aggregation and agglomeration. Human exposure is primarily to carbon black particles in aggregate and agglomerate forms. Average aggregate particle diameters in several commercially produced carbon blacks range from 50 to 600 nm and the more loosely associated agglomerates can reach up to many micrometers in diameter. The majority of carbon blacks currently manufactured have small quantities ($< 1\%$) of organic compounds, including polycyclic aromatic hydrocarbons, adsorbed onto their surface.

About 90% of carbon black is used in rubber products, predominantly in tyres. Carbon black is also used as a pigment in inks, paints and coatings and in plastics.

Exposures to carbon black vary markedly between and within any production facility and over time. The highest levels of exposure are experienced by packers and site cleaners. Some studies before 1970 found that extremely high levels of exposure to carbon black could have occurred in the manufacturing industry. Exposure studies in this industry in the USA and western Europe after the late 1970s found personal geometric mean exposures to inhalable dust to be less than 5 mg/m^3. By the mid- to late 1990s the geometric mean levels of inhalable dust were below 2 mg/m^3. The geometric mean levels of respirable dust were below 0.5 mg/m^3. No data were available that would allow the characterization or quantification of exposure to ultrafine primary particles. Exposure in the user industries is difficult to assess because of the lack of data and concomitant exposure to many other particles but exposure levels are assumed to be lower, with the possible exception of workers who handle carbon black in these industries. Exposure to carbon black does not occur during the use of products in which carbon black is bound to other materials, such as rubber, printing ink or paint.

5.2   Human carcinogenicity data

The greatest potential for elucidating the carcinogenicity of carbon black is in the carbon black production industry where it has been the primary industrial exposure. Cohort studies of carbon black production workers have been conducted in Germany, the United Kingdom and the USA.

A cohort study was conducted among blue-collar workers in a long-standing, large German carbon black production plant. When mortality was compared with regional rates, there was an approximate doubling of risk for lung cancer. Exposure was assessed using full work history records from the plant and expert judgements. Further, company medical records provided some information on tobacco smoking for most of the workers. Compared with the lowest exposure group, and after adjusting for smoking, there was no indication that workers with several indices of or average exposure to carbon black had higher mortality. However, the precision of these subgroup risk estimates was low. There was no excess mortality from cancer at most other sites, including oesophagus, stomach and urinary bladder, although the numbers were small.

Another group of investigators analysed the same German cohort of carbon black workers using different methods. They confirmed that there was no exposure–response relationship within the cohort between estimated exposure to carbon black and lung cancer. After accounting for regional variations in cancer and different methods of adjustment for tobacco smoking and other exposures, the overall risk for lung cancer was slightly elevated, although the Working Group was not persuaded that all the adjustments were warranted.

The study of workers in five carbon black production facilities in the United Kingdom involved a large group with a long follow-up. When compared with national mortality rates, there was a clear excess of mortality from lung cancer. Although tobacco smoking histories were not known, there was no corresponding significant excess of other diseases known to be associated with smoking. The excess risk was manifest in two of five factories. Exposure was assessed using last job from worker records and a job–exposure matrix based on expert judgement and measurements from two of the five plants. When adjusted for age and divided into four subgroups based on cumulative exposure levels, relative risk did not increase monotonically with increasing exposure, although the two highest exposure categories showed higher relative risks than the two lowest categories. There was no significant excess risk for cancer at any other site.

A study in the USA included a large cohort of workers from 18 plants with good ascertainment of cohort members and effective mortality follow-up over a long period of time. There was no indication of excess risk for cancer at any of the sites reported. There was no indication that long-service workers had higher risks than short-service workers. For most types of cancer, including lung cancer, the numbers of deaths observed did not exceed the numbers expected on the basis of national rates. No results were provided taking into account various levels of exposure to carbon black or tobacco smoking habits.

CARBON BLACK   187

Additional evidence is provided by studies of workers who were exposed to carbon black in some other industries.

Within a large cohort of German rubber industry workers, an attempt was made to assess exposure to carbon black. The exposure assessment was rather crude. In statistical analyses of carbon black that did not include other exposure variables as potential confounders, there were significant excess risks for cancers of the larynx, lung and stomach. When exposure to nitrosamines, asbestos and talc were considered, the excess risks were no longer statistically significant.

A cohort study was carried out among workers in the USA to assess cancer risks due to exposure to formaldehyde in 10 participating plants that were spread across several industries. To control for confounding and modification of effect by other exposures, exposures of workers to various other chemicals, including carbon black, were assessed by industrial hygienists. Overall, among carbon black-exposed workers, there was a slight non-significant excess risk for lung cancer. There was no clear trend by duration of exposure.

A study of Italian dockyard workers was based on the undocumented but reasonable premise that those who unloaded and carried bags of carbon black experienced higher exposures. Apart from mesothelioma and malignant melanoma, neither of which were probably attributable to exposure to carbon black, only one site—urinary bladder cancer—showed some evidence of a statistically significant excess. For lung cancer, stomach cancer and cancer at several other sites, there was no indication of excess risk.

In a community-based case–control study in Montréal, Canada, interviews were designed to obtain detailed lifetime job histories and information on potential confounders. Potential occupational exposures were identified for each job description; carbon black was among the exposures assessed. Few if any of the exposed subjects had worked in the manufacture of carbon black. Many workers were exposed to carbon black in bound matrices such as paint or rubber. It is probable that workers exposed to carbon black in this study were exposed to lower levels than those in other studies. There was an indication of excess risk associated with exposure to carbon black for cancers of the lung, oesophagus and kidney, but not for cancer of the stomach, urinary bladder or at other sites.

A Swedish community-based case–control study reported a non-significant increased risk for urothelial cancer for men exposed to carbon black.

Seven studies were considered to be informative for lung cancer of which three were among carbon black production workers. The Working Group considered the studies of carbon black producers in Germany, the United Kingdom and the USA, to be the most informative for assessing cancer risk. The two studies from Germany and the United Kingdom indicated an excess risk compared with external references. Confounding by tobacco smoking could not be excluded, although it was unlikely to have explained the entire excess risk. However, in both cohorts, internal analyses by level of exposure to carbon black gave equivocal but mainly null results. The study of carbon black workers in the USA suggested no excess mortality, but did not assess risk by level of exposure. In

studies that assessed risks for lung cancer among user industries, the most informative study of German rubber workers showed some indication of excess risk that disappeared when asbestos and talc were adjusted for in the analysis. Of the remaining studies, two others showed non-significant excesses (formaldehyde cohort in the USA and the Canadian community-based case–control study) and one showed no excess risk for lung cancer linked to the handling of carbon black (Italian dockworkers).

For cancers of the urinary bladder, kidney, stomach and oesophagus, isolated results indicate excess risks, but these are not sufficient to support an evaluation of human carcinogenicity. There is no evidence of an effect of carbon black for other cancer sites.

5.3   Animal carcinogenicity data

Two different carbon black products were tested by inhalation exposure in two studies in female rats and in one study in rats of each sex. Significant increases in the incidence of malignant lung tumours or of benign and malignant lung tumours combined were observed in female rats in all three studies. In addition, an increased incidence of lesions described as benign cystic keratinizing squamous-cell tumours or squamous-cell cysts was observed. In one study in female mice exposed by inhalation, carbon black did not increase the incidence of respiratory tract tumours.

In two studies of intratracheal administration to female rats using two types of carbon black and in one study using one type, an increased incidence of malignant lung tumours or of benign and malignant lung tumours combined was observed.

In several experiments of dermal application in mice that used various carbon blacks, no carcinogenic effect on the skin was observed; the dermal application of benzene extracts of several carbon blacks resulted in skin tumours.

In one study in male and female mice using the same types of carbon black by subcutaneous injection, a carbon black that contained demonstrable quantities of carcinogenic polycyclic aromatic hydrocarbons produced local sarcomas, whereas a carbon black in which no polycyclic aromatic hydrocarbon was detected did not produce such sarcomas. In several experiments in mice, solvent extracts of carbon black produced sarcomas following subcutaneous injection.

No adequate study of the carcinogenicity of carbon black administered by the oral or intraperitoneal route was available.

5.4   Mechanistic considerations and other relevant data

The deposition pattern of carbon black particles depends on the particle size (aerodynamic or thermodynamic) and on the anatomical and physiological characteristics of the host. The deposition fraction of carbon black influences the dose to a given region of the respiratory tract. Some studies described the retention of carbon black in the respiratory tract of exposed workers, as well as the health effects of these exposures. For example, lung tissues from workers in carbon black factories have been shown to contain

CARBON BLACK 189

deposits of carbon black. Lung diseases or conditions may influence the deposition and retention of particles such as carbon black. For instance, asthmatics had a higher total deposition of ultrafine carbon particles in the respiratory tract compared with healthy individuals. The amount of carbon black deposited can also increase with increasing minute volume, for instance in individuals taking exercise or during heavy work loads. High retained mass lung burdens and decrease in lung clearance have been observed in miners.

Non-cancer respiratory effects in carbon black workers that have been reported include cough, sputum production, bronchitis, chest radiographic opacities (e.g. pneumoconiosis) and decrements in lung function.

Many studies have been conducted on the deposition and retention kinetics of inhaled carbon particles following intratracheal instillation or inhalation in rodent species. In general, all rodent species investigated displayed evidence of rapid clearance of inhaled carbon particles when exposure concentrations did not result in lung overload (impaired clearance resulting in accumulation of particles in the lung tissue). Experimental studies of ultrafine particles of carbon black have shown that rodents experience dose-dependent impairment of alveolar macrophage-mediated clearance, which occurs at lower mass doses of ultrafine particles than these of with larger particles. Overloading has been observed in rats, mice and hamsters exposed to carbon black. Hamsters appear to exhibit the most efficient clearance of carbon black particles compared with rats and mice. Adverse lung responses to inhaled carbon black (pulmonary inflammation and epithelial injury) increase significantly with the increased retained lung dose of carbon black. Fine and ultrafine carbon black particles can translocate beyond the lungs to other organs.

Several toxic effects of carbon black have been reported in rodent species. They toxic were dose-dependent and included inflammation, lung epithelial cell injury and lung lesions that were more severe and prolonged in rats than in mice and hamsters. Exposure to carbon black particles modulates the immune system. In-vitro studies showed evidence that carbon black particles can generate reactive oxygen species in cell-free systems, increase the production of tumour necrosis factor-α and activate serum factors such as complement.

The genotoxicity of carbon black has been evaluated and found to be negative in most assays for mutagenicity. In one study in rats exposed to carbon black by inhalation, the *Hprt* mutant frequency was elevated in lung epithelial cells following a 15-week exposure. A significant increase in pro-mutagenic 8-oxo-7,8-dihydro-2′-deoxyguanosine induction was observed in the lungs of rats exposed for 13 weeks to one type of carbon black. Carbon black did not induce a significant increase in DNA adducts in the peripheral lung tissue of rats after 2 years of inhalation exposure. K-*ras* mutations were found in one of 18 neoplasms analysed from carbon black-exposed rats; no exposure-related *Tp53* mutation was found. In vitro, rat lung epithelial cells exposed to bronchoalveolar lavage fluid from rats instilled with carbon black showed an increase in *Hprt* mutant frequency. Most in-vitro mutagenicity studies of carbon black have proved negative.

6. Evaluation and Rationale

6.1   Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of carbon black.

6.2   Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black.

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black extracts.

6.3   Overall evaluation

Carbon black is *possibly carcinogenic to humans (Group 2B)*.

6.4   Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as the evidence on potential mechanisms through which carbon black may cause cancer in humans.

The human epidemiological evidence was inconsistent. Two of the three studies of carbon black production workers observed excess risk for lung cancer and other studies provided mixed evidence for an increased risk for lung and other cancers. The few studies that assessed exposure–response for lung cancer, including the two that observed excess risks compared with the general population, provided weak or inconclusive evidence of a dose–response. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether carbon black causes cancer in humans.

Three studies of female rats that inhaled carbon black and three additional studies of female rats exposed intratracheally found significant increases in the incidence of malignant lung tumours, providing *sufficient evidence* that carbon black can cause cancer in animals. Solvent extracts of carbon black were used in one study of rats in which skin tumours were observed after dermal application and several studies of mice in which sarcomas were seen following subcutaneous injection, providing *sufficient evidence* that carbon black extracts can cause cancer in animals.

The Working Group considered a large body of mechanistic information. For lung cancer in rats, it was concluded that a sequence of events that starts with impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury and

CARBON BLACK   191

production of reactive oxygen species that eventually lead to mutations, was well supported by experimental evidence, although some data also supported alternative pathways. High retained mass lung burdens and decreased lung clearance have been observed in coal miners, which led the Working Group to conclude that animal cancer data obtained under conditions of impaired lung clearance are relevant to humans. There was a minority opinion in the Working Group that would support the classification of carbon black in Group 2A, and invoked the analogy with quartz particles, which are carcinogenic in the lung of rats and humans. However, based on current evidence, the Working Group considered that the degree to which all elements of the above-mentioned mechanism may operate in humans is not clear and, thus, the mechanistic information did not alter the overall evaluation of Group 2B.

TITANIUM DIOXIDE

Titanium dioxide was considered by a previous Working Group in October 1988 (IARC, 1989). Since that time, new data have become available, and these have been included in the present monograph and taken into consideration in the evaluation.

1. Exposure Data

1.1   Chemical and physical data

1.1.1   *Nomenclature*

Chem. Abstr. Services Reg. No.: 13463–67–7, titanium dioxide; 1317–70–0, anatase titanium dioxide; 1317–80–2, rutile titanium dioxide
Chem. Abstr. Name: Titanium dioxide
IUPAC Systematic Name: Titanium dioxide
Synonyms: CI: 77891; dioxotitanium oxide; E 171; NCI-CO4240; Pigment White 6; titania; titanic oxide; titanium oxide; titanium (IV) oxide; titanium peroxide

1.1.2   *Molecular formula and relative molecular mass*

TiO_2 Relative molecular mass: 79.90

1.1.3   *Chemical and physical properties of the pure substance*

Description: Fine white powder (Windholz, 1983)
Crystal structure
Four naturally occurring titanium dioxide polymorphs exist: rutile, anatase, brookite and titanium dioxide(B) (Banfield & Veblen, 1992). Anatase and rutile are tetragonal, brookite is orthorhombic and titanium dioxide(B) is monoclinic. In all four polymorphs, titanium is coordinated octahedrally by oxygen, but the position of the octahedra differs between polymorphs. The structure of rutile is the most dense and its unit cell is the smallest. Anatase has four formula units per unit cell with $a = 0.379$ nm and $c = 0.951$ nm; rutile has two with $a = 0.459$ nm and $c = 0.296$ nm; brookite has eight with $a = 0.917$ nm, $b = 0.546$ nm and $c = 0.514$ nm; and titanium

–193–

dioxide(B) has eight with a = 1.216 nm, b = 0.374 nm, c = 0.651 nm and β = 107.29°
(Banfield & Veblen, 1992). Only the structures of rutile (titanium dioxide-rutile) and
anatase (titanium dioxide-anatase) are reported in commercial products.

Density of ideal minerals: Anatase, 3.79 g/cm^3; rutile, 4.13 g/cm^3; brookite,
3.99 g/cm^3; and titanium dioxide(B), 3.64 g/cm^3 (Banfield & Veblen, 1992)

Refractive index: Anatase, 2.561, 2.488; rutile, 2.605–2.616, 2.890–2.903; and
brookite, 2.583, 2.700 (Phillips & Griffen, 1981)

Hardness on Moh's scale: Anatase, 5.5–6; rutile, 6–6.5; and brookite, 5.5–6 (Harben
& Kuzvart, 1996)

Solubility: Soluble in sulfuric acid and alkalis; insoluble in water (Weast, 1985)

Spectroscopy: X-Ray diffraction patterns for anatase and rutile are available from the
International Center for Diffraction Data (2005), which maintains the powder
diffraction file.

Chemical composition: Natural rutile, anatase and brookite contain impurities of up to
≈2% that include iron, chromium, vanadium, aluminium, niobium, tantal, hafnium
and zirconium (Heaney & Banfield, 1993) and account for slight variations in density,
colour and indices of refraction. Since most commercial titanium dioxide is
manufactured from natural material by dissolution of the parent mineral and
reprecipitation as fine particles with the structure of anatase or rutile (referred to as
titanium dioxide-anatase or titanium dioxide-rutile), most but not all of these chemical
impurities are generally removed.

Other characteristics: Titanium dioxide is an ultraviolet (UV)-activated catalyst, and
organic polymers that are in contact with it degrade under UV radiation. Anatase is
10 times more active than rutile and responds to slightly different wavelengths
(Braun, 1997).

1.1.4   *Technical products and impurities*

Trade names for titanium dioxide include Aeroxide, A-Fil Cream, Atlas white
titanium dioxide, Austiox, Bayertitan, Calcotone White T, Comet, Cosmetic White C47–
5175, Cosmetic White C47–9623, C-Weiss 7, Flamenco, Hitox, Hombitan, Hombitec,
Horse Head A-410, Horse Head A-420, Horse Head R-710, Kemira, KH 360, Kronos
titanium dioxide, Levnox White RKB, Pretiox, Rayox, Runa RH20, Rutile, Rutil RC,
Rutiox, Tichlor, Tiofine, TiO2 Hombitan, Tiona T.D., Tioxide, Tipaque, Ti-Pure, Ti-
Select, Titafrance, Titan, Titania, Titandioxid, Titanium White, Titanox, Titanox 2010,
Trioxide(s), Tronox, Tytanpolr, Unitane products (various), UV-Titan, 1700 White and
Zopaque.

(a)   *Particle size*

Titanium dioxide particles are referred to as primary, aggregates or agglomerates.
Primary particles are single crystals that are bound by crystal planes. Aggregates are

sintered primary particles that are connected by crystal faces. Agglomerates are multiple primary particles and aggregates that are held together by van der Waal's forces.

Scattering of light by titanium dioxide is maximized in particles that are 0.2–0.3 μm in diameter, and most commercial products that are used as pigments have modal primary particle sizes within this range. The range of ultrasonically dispersed primary particles and aggregates is narrow, and generally ranges from <0.1 to 0.5 μm (Braun, 1997; Linak *et al*., 2002; Swiler, 2005). A recent study showed that commercial pigments contain almost no particles <0.1 μm. This range may not apply to bulk material, which contains aggregates that are not broken down during industrial use (Braun, 1997).

Non-pigmentary titanium dioxide is composed of either uncoated manufactured titanium dioxide (both titanium dioxide-anatase and titanium dioxide-rutile) or ground natural rutile. In general, these products contain coarser particles than pigmentary titanium dioxide (Linak *et al*., 2002).

Ultrafine titanium dioxide particles (nanoparticles) range in size from 1 to 150 nm (Linak *et al*., 2002), with a modal primary particle size of 10–50 nm. They are generated by sol-gel synthesis and the wide variation in their morphology and size is controlled by the pH of the gel.

Primary particles generally form aggregates and agglomerates and are not normally found as discrete particles. In commercial products, the particle size of pigmentary and ultrafine material is approximately equal because of aggregation and agglomeration (American Chemistry Council, 2005).

Titanium dioxide has also been produced as engineered nanomaterials, which may be equidimensional crystals or sheets and are composed of either titanium dioxide-rutile or titanium dioxide-anatase. A tubular structure has been produced from scrolling layers of titanium dioxide-anatase, which results in fibres with an outer diameter of about 6 nm and an inner tube of about 3 nm (Barnard *et al*., 2005). Non-scrolled nanofibres have also been produced from titanium dioxide-anatase and titanium dioxide(B) with diameters of 20–100 nm and lengths of 10–100 μm (Pavasupree *et al*., 2005).

(b)   Types of titanium-dioxide pigment

According to the American Society for Testing and Materials (ASTM, 1988) D476–84 standard, four types of titanium dioxide pigment exist (Schurr, 1981; Fisher & Egerton, 2001):

Type I (94% titanium dioxide min.) is a titanium dioxide-anatase pigment that chalks [forms a layer of loose pigment powder on the surface of weathered paint film] freely and is used in white interior and exterior house paints.

Type II (92% titanium dioxide min.) is a titanium dioxide-rutile pigment that has a medium resistance to chalking and is used in varying amounts in all types of interior paints, enamels and lacquers.

Type III (80% titanium dioxide min.) is also a titanium dioxide-rutile pigment that has a medium resistance to chalking and is used principally in alkyd and emulsion flat-wall paints.

Type IV (80% titanium dioxide min.) is another titanium dioxide-rutile pigment that has a high resistance to chalking; it is used in exterior paints and has excellent durability and gloss retention.

The Japanese grading system, the JIS K5116–1973, specifies four grades of titanium dioxide-rutile, three of which contain at least 92% titanium dioxide and the fourth contains a minimum of 82%. The type of coating in each grade is also specified (Fisher & Egerton, 2001).

(c)   Extenders, impurities and coatings

Titanium dioxide extenders were used in commercial pigments in the past, but are not generally employed now. Calcium sulfate (Braun, 1997) and barium sulfate (Fisher & Egerton, 2001) were commonly used during the early years of production, and other materials that may have been used as extenders for white pigment include calcium carbonate, alumina, silica and kaolin (Linak *et al.*, 2002).

Titanium dioxide-anatase pigments may contain titanium dioxide-rutile. Before coating, titanium dioxide-anatase produced by the sulfate process contains both phosphorous and sulfate that are concentrated at the particle surface. In addition, uncoated titanium dioxide-anatase pigments retain about 0.3% niobium pentoxide and 0.3% phosphorus pentoxide from the ore and up to 0.2% alumina that is added during manufacture (Braun, 1997).

Prior to coating, titanium dioxide-rutile pigments that are produced by chlorination contain about 1% alumina, which is concentrated at the surface of the particles (Braun 1997), but not titanium dioxide-anatase.

With the exception of non-pigmentary titanium dioxide such as ground rutile and titanium dioxide-anatase that are used as food additives, all commercially produced titanium dioxide is coated by a variety of oxides and oxyhydrates by aqueous precipitation techniques. These coatings improve dispersibility, dispersion stability, opacity, durability and gloss. They form a barrier between the titanium dioxide and organic substances, such as those found in paints, and prevent contact catalysis. In some cases, organic or silicone treatments may be added after initial coating. Titanium dioxide-rutile pigments generally contain 1–15% of coatings and titanium dioxide-anatase pigments contain 1–5% of coatings. The most common coatings are composed of oxyhydrates and oxides of aluminium and silicone. Oxides and oxyhydrates of zirconium, tin, zinc, phosphorous, cerium and boron are also used (Linak *et al.*, 2002). Table 1.1 (American Chemistry Council, 2005) gives the types of coating that are used in decreasing order of importance.

The thickness of these coatings is variable but may be only a few atom layers. They are generally coherent over the surface of the titanium dioxide particle (American Chemistry Council, 2005), but some titanium oxide and titanium hydroxide may also be present on the surfaces (Braun, 1997). The thinness of the coatings precludes most techniques of structural analysis and their atomic structure therefore remains largely unknown (Braun, 1997). The composition (but not necessarily the atomic structure) of the

alumina coatings are γ-AlOOH (bohemite), α-AlOOH (diaspor) and γ-Al(OH)$_3$ (hydrargillite). The silica coatings may be fluffy, and consist of polymerized silicic acid or a dense, true shell of glass. Ultrafine titanium dioxide is also coated; examples of coatings are given in Table 1.2.

Coating with alumina and silica can more than double the surface area (Braun, 1997). The surface area of untreated pigment ranges from 8 to 10 m^2/g, while treated pigment surface areas generally span 8–19 m^2/g and matt-finish pigments (that have high levels of alumina) can extend up to 35 m^2/g. Surface areas of the ultrafine products are in the range of 35–100 m^2/g (American Chemistry Council, 2005).

Titanium dioxide-coated surface and pigments are hydrophilic; those coated with silicones are not used as pigment because they are hydrophobic.

Table 1.1. Types of coating used for common grades of titanium dioxide pigment (normally titanium dioxide-rutile)

Surface treatment type	Composition, range (wt %)	Application
Alumina/TMP	Al$_2$O$_3$, 1.0–5.5 Total carbon, <0.3	Paint/coatings
Alumina/zirconia/TMP	Al$_2$O$_3$, 1.0–5.0 ZrO$_2$, 0.3–1.0 Total carbon, <0.3	Paint/coatings
Alumina/silica/siloxane	Al$_2$O$_3$, 1–6 SiO$_2$, 0.3–3 Total carbon, <0.3	Plastics
Alumina/silica/TMP	Al$_2$O$_3$, 1.0–6.0 SiO$_2$, 0.5–13.0 Total carbon, <0.3	Paint/coatings/plastics
Alumina/TME	Al$_2$O$_3$, 1.0–3.5 Total carbon, <0.3	Paint/coatings
Alumina/zirconia/TME	Al$_2$O$_3$, 1.0–5.0 ZrO$_2$, 0.3–1.0 Total carbon, <0.3	Paint/coatings
Alumina/silica/TME	Al$_2$O$_3$, 1.5–5.0 SiO$_2$, 1.5–3.5 Total carbon, <0.3	Paint/coatings
Alumina/silica/silane	Al$_2$O$_3$, 1.0–6.0 SiO$_2$, 0.3–3 Total carbon, <0.3	Plastics

From American Chemistry Council (2005)
TME, trimethylol ethane; TMP, trimethylol propane; wt, weight

198   IARC MONOGRAPHS VOLUME 93

Table 1.2. Relative proportion[a] of the production of common grades of ultrafine titanium dioxide used in sunscreens with different types of coating

Organic	Inorganic				
	None	Silica 5–25%	Alumina 1–25%	Silica 1–10% + alumina 5–15%	Sodium meta-phosphate 1–5%
None	2	4	3	4	1
Stearate 5–15% as carbon			16		
Butyl glycol dicaprylate 60% + stearate 5%		1			
Methicone max. 11%		1	1		
Dimethicone 1–10%			2	4	
Dimethicone/siloxane 2% as SiO_2			2		
Dimethicone/methicone copolymer 1–10%	2	2		4	
Simethicone 5% (as SiO_2) + water 13%	2				
Trimethylsiloxysilicone 1–10%				4	
Polyvinyl-pyrrolidone max. 3%			1		
Alkyl silane 2.7–3.7% as carbon	1				
Glycerin max. 1%			1		
Alginate 1–5%				1	

From American Chemistry Council (2005)

[a] 16=high, 1=low

1.1.5   *Analysis*

Exposure to particulates in occupational environments is generally determined gravimetrically. The behaviour of titanium dioxide in air and its deposition in the respiratory tract upon inhalation are important factors in human exposure, and are determined by the aerodynamic diameter of the particles. The aerodynamic diameter can be measured by impactors and is dependent upon the geometric diameter, [material] density and shape [factor] of the aggregates. Most commonly, the size distribution of airborne particles is expressed as the mass median aerodynamic diameter (MMAD) and the geometric standard deviation. Several dust fractions are often identified, namely, 'total' dust, inhalable dust and respirable dust.

Inhalable dust approximates the fraction of airborne material that enters the nose and mouth during breathing and is therefore available for deposition anywhere in the respiratory tract (International Standards Organization, 1995; Health and Safety Executive, 2000). The inhalable fraction depends on the prevailing movement of air around the exposed person and whether breathing is by the nose or mouth. It is, however, possible to define target specifications for sampling instruments that approximate the inhalable fraction and these are provided by the International Standards Organization (1995). In the United Kingdom, the standard sampling devices for measuring inhalable dust are the multiorifice sampler and the Institute of Medicine (IOM) sampler (Health and Safety Executive, 2000).

Respirable dust approximates the fraction of airborne material that penetrates the gas-exchange region of the lung. The respirable fraction varies between individuals; however, it is possible to define a target specification for sampling instruments that approximates the respirable fraction for an average person (International Standards Organization, 1995). Respirable dust is generally collected using a cyclone preselector (Health and Safety Executive, 2000).

The term 'total' dust refers to total particulates that are represented (in North America at least) by the material that is collected by a closed-face three-piece plastic sampling cassette that holds a 37-mm filter (Eller & Cassinelli, 1994). The term 'total' dust is not equivalent to all airborne dust; in fact, measurements of inhalable dust by the IOM sampling head are 1.0–2.5 times higher than 'total' dust levels using a closed-face 37-mm filter cassette, depending on the aerodynamic diameter of the particles (Werner *et al*., 1996).

Analysis of different types of coatings is accomplished by transmission electron microscopy equipped with energy-dispersive X-ray spectroscopy.

1.2   Production and use

1.2.1   *Production*

The manufacture of pure titanium white for use as a pigment (anatase form) was first reported in 1923 in France. The growth of the production and use of titanium white pigments began in the early 1930s and continued until recently, but the rate has now decreased. In 2004, worldwide production was estimated at 4.4 million tonnes (Swiler, 2005).

(a)   Sources

Titanium dioxide pigments are manufactured from a variety of ores that contain ilmenite ($FeTiO_3$), rutile, anatase and leucoxene ($TiO_2.xFeO.yH_2O$), which are mined from deposits located throughout the world. Titanium may also be recovered from slag produced during iron smelting and from synthetic rutile produced from ilmenite.

Large deposits of titanium dioxide occur in association with igneous rocks and as heavy mineral deposits in unconsolidated sands (Garnar & Stanaway, 1994; Chang, 2002). Major igneous deposits are found in Brazil, Canada, Norway, the Russian Federation and the Ukraine (Chang, 2002).

Important heavy mineral sands are found along the eastern and western coasts of Australia, the eastern coast of South Africa, the southeastern coast of the USA, the west coast of South Island, New Zealand, the eastern coast of China, the northeastern coast of Sri Lanka, at various locations along the southern coast of India, in coastal Malaysia and in alluvial deposits in Sierra Leone and China (Chang, 2002).

Anatase, brookite and titanium dioxide(B) are common minor constituents in soils and sediments, particularly those derived from titanium-rich rocks. Rutile is a common accessory mineral in a wide variety of crustal and mantle-derived rocks and in sediment and sedimentary rocks (Heaney & Banfield, 1993).

Ilmenite is found in beach sand in existing or fossil coastlines and is an important raw material in titanium dioxide production. Surface processes alter the ilmenite in these deposits to produce submicroscopic mixtures of minerals that include anatase, rutile and amorphous phases. Mixtures that contain as much as 90% titanium dioxide are referred to as leucoxene. Leucoxene is recovered from some deposits and treated separately. However, the quantities produced are small in comparison with those of ilmenite. The concentrates obtained from ilmenite sand, which are depleted of iron, are generally richer in titanium dioxide than those from the massive deposits. Other elements in these concentrates include magnesium, manganese and vanadium that are present in the ilmenite, and aluminum, calcium, chromium and silicon (Kischkewitz *et al*., 2002).

The second most commonly available ore is the buff-coloured mineral rutile, which contains about 95% titanium dioxide with smaller amounts of iron and other impurities. The rutile contained in primary rocks cannot be extracted. Only sands in which rutile is accompanied by zircon and/or ilmenite and other heavy minerals can be used as raw materials. Rutile sands are mostly found in Australia, Sierra Leone and South Africa. The importance of mineral rutile to the titanium dioxide industry is waning. In the 1970s, it accounted for 20% of the feedstock, but now accounts for less than 10% due to diminishing reserves (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

Anatase, like rutile, is a modification of titanium dioxide. The largest reserves of this mineral are found in carboniferous intrusions in Brazil. Techniques for preparation of the ore produce concentrates that contain 80% titanium dioxide, and further concentration to 90% titanium dioxide is possible by treatment with hydrochloric acid (Kischkewitz *et al*., 2002).

(b)   Processing

There are five stages in the manufacture of pigmentary titanium dioxide. First, titanium dioxide ore is converted to either aqueous titanyl sulfate solution or anhydrous titanium tetrachloride. These intermediates are then converted to crystalline, size-specific pigmentary particles of titanium dioxide-rutile or titanium dioxide-anatase. The pigment

is coated, in some cases involving a grinding step, and then filtered, washed and dried. Finally, the pigment agglomerates may be ground to reduce their size without breaking the primary titanium dioxide particles (Braun, 1997).

Most ores are concentrated or otherwise processed to increase the titanium dioxide content before they are suitable as a raw material for pigment production. Impurities such as iron and alkaline earth elements colour the ores from buff to black and must be removed to obtain a clean white titanium dioxide pigment (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

Direct use of ilmenites has decreased due to their high iron content. A digestion process is employed to produce iron sulfate heptahydrate from ilmenite. When iron sulfate is not required as a product, metallurgical recovery of iron from iron-rich ilmenites and production of a titanium-rich slag are increasingly being used (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

Titanium dioxide pigment is produced from titanium mineral concentrates by either the chloride process or the sulfate process. In the sulfate process, ilmenite or titanium slag is reacted with sulfuric acid. Titanium hydroxide is then precipitated by hydrolysis, filtered and calcined. In the chloride process, rutile is converted to titanium tetrachloride by chlorination in the presence of petroleum coke. The titanium tetrachloride is oxidized by air or oxygen at about 1000°C, and the resulting titanium dioxide is calcined to remove residual chlorine and any hydrochloric acid that may have formed in the reaction. Aluminium chloride is added to the titanium tetrachloride to ensure that virtually all the titanium is oxidized into the rutile crystal structure. Although either process may be used to produce pigment, the decision to use one process instead of the other is based on numerous factors, including the availability of raw materials, freight and waste disposal costs. In finishing operations, the crude form of the pigment is milled to produce a controlled distribution of particle size and the surface is treated or coated to improve its functional behaviour in different media. Typical surface treatments include alumina, organic compounds (e.g. polyols, esters, siloxanes, silanes) and silica (Kischkewitz *et al*., 2002; Gambogi, 2003).

Each producer of titanium dioxide has its own purity requirements and hence places different values on certain physical properties. For example, Japanese producers tend to prefer ilmenite which has a higher ferrous oxide content but a lower titanium dioxide content than the ores generally favoured by European producers (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

(c)   Capacity, production and consumption

In 2004, world production of titanium mineral concentrates had increased to 5.2 million tonnes from 4.6 million tonnes in 2000. Approximately 95% is used as feedstock for titanium dioxide and the remainder is used in titanium metal alloys. In 2004, the leading supplier of titanium feedstock was South Africa (25%), followed by Australia (21%), Canada (14%), China (8%), the Ukraine (7%) and Norway (7%) (Linak & Inoguchi, 2005).

Approximately 60 plant sites worldwide (outside of China) produce titanium dioxide, with an average annual capacity of 60 000 tonnes. Table 1.3 presents world titanium dioxide capacity by region and process for 1993, 1998, 2002 and 2005 (Linak & Inoguchi, 2005).

In recent years, most increases in capacity have been through the development of small plants in China and other less developed regions. Until recently, global capacity had been growing faster than demand, resulting in oversupply and erosion of prices. In real terms, prices have been decreasing on average by about 1% per year for the past 20 years (Linak & Inoguchi, 2005).

For environmental, economic and qualitative reasons, chloride process plants continue to be favoured over sulfate plants in industrialized countries, particularly for new production facilities. Operators of sulfate process plants have had to invest in waste acid recycling facilities to extend operating lives. In addition, the production of rutile pigment from the chloride process has increased (Linak & Inoguchi, 2005).

Titanium dioxide is used in more than 170 countries. The major exporting regions are North America and Australia, and most of the countries in the rest of the world are net importers. Table 1.4 presents world supply and demand for titanium dioxide in 1997, 2001 and 2004 (Linak & Inoguchi, 2005).

1.2.2   *Use*

Titanium dioxide is valued for its opacifying strength (commonly called hiding power) and brightness. Other important features of titanium dioxide pigments are excellent resistance to chemical attack, good thermal stability and resistance to UV degradation. Rutile pigment is more resistant to UV light than anatase, and is preferred for paints, plastics, especially those exposed to outdoor conditions, and inks. Anatase pigment has a bluer tone than the rutile type, is less abrasive and is used mainly in indoor paints and in paper, ceramics, rubber and fibres manufacture. Both rutile and anatase pigments can be made more resistant to photodegradation by coating the pigment particles, which also improves their dispersibility, dispersion stability, opacity and gloss. Usually alumina, silica, zirconia or a combination of these is used; silica is most effective in retarding the photoactivity of the pigment, while alumina is most effective in enhancing dispersibility and binder compatability. Generally, rutile pigments contain 1–15% coating and anatase pigments contain 1–5%. The higher levels of coating are given to pigments that are typically used for applications such as flat (low-gloss) paints (Linak & Inoguchi, 2005).

The major consumer industries for titanium dioxide pigments are mature sectors in high-resource countries where they are used for surface coatings, paper and paperboard and plastics. Therefore, consumption of titanium dioxide tends to parallel general economic trends. Paint and coating applications have the largest global use, and plastics and paper account for most of the remainder. World consumption of titanium dioxide by end-use in 2001 was: coatings, 55%; plastics and rubber, 24%; paper, 12%; printing inks, 3%; and other, 6%; that in 2005 was: coatings, 58%; plastics and rubber, 23%; paper, 11%;

Table 1.3. World capacity for titanium dioxide (thousand tonnes, gross weight)

Region	1993			1998			2002			2005		
	S	C	Total	S	C	Total	S	C	Total	S	C	Total
North America	202	1288	1488	178	1436	1614	134	1656	1790	80	1717	1797
Central and South America	55	0	55	60	0	60	60	0	60	96	0	96
Western Europe	875	317	1192	913	405	1318	925	472	1397	862	547	1409
Central and eastern Europe	195	0	195	203	0	203	217	0	217	234	0	234
Africa and Middle East	35	50	85	40	80	119	40	100	140	25	100	125
Japan	270	50	319	272	52	324	259	68	327	240	68	308
China	–	–	–	–	–	–	258	408	666	658	15	673
Oceania and other Asia	224	114	338	291	184	475	–	–	–	141	404	545
Total	1856	1819	3672	1957	2157	4113	1893	2704	4597	2336	2857	5187

From Linak & Inoguchi (2005)
C, chloride process; S, sulfate process

TITANIUM DIOXIDE

Table 1.4. World production and consumption of titanium dioxide (thousand tonnes, gross weight)

Region	1997		2001		2004	
	P	C	P	C	P	C
North America						
Canada	75	105	68	90	76	104
Mexico	102	37	124	65	124	64
USA	1340	1129	1340	1100	1511	1162
Central and South America						
Brazil	79	108	78	111	80	124
Other	0	60	0	60	0	85
Western Europe	1113	1099	1150	1100	1254	1183
Central and eastern Europe	136	125	155	155	155	155
Africa and Middle East						
Saudi Arabia	50	10	55	10	90	30
Other Middle East	0	60	0	65	0	120
South Africa	30	25	30	20	20	28
Other Africa	0	15	0	35	0	45
Japan	241	269	257	246	253	238
Oceania and other Asia						
Australia	160	40	181	66	200	40
China	102	170	147	256	350	540
India and Pakistan	50	70	44	77	52	82
Indonesia	–	–	–	–	0	49
Malaysia	–	–	50	28	50	15
Philippines	–	–	–	–	0	33
Republic of Korea	35	100	42	118	40	120
Singapore	–	–	41	16	45	30
Southeast Asia	77	145	–	–	–	–
Taiwan (China)	68	71	123	66	120	66
Thailand	–	–	–	–	0	71
Other	–	–	0	108	0	29
Total	3658	3638	3885	3792	4420	4423

C, consumption; P, production
From Linak & Inoguchi (2005)

and other, 8% (Linak & Inoguchi, 2005). Some other uses of titanium dioxide are in catalysts, ceramics, coated fabrics and textiles, floor coverings and roofing granules (Gambogi, 2005; Swiler, 2005).

Despite their lower price, anatase-grade pigments account for only 10% of total global production. About two-thirds of the total anatase supply is used in markets where quality is less important, such as paper, low-priced emulsion paints, or tiles and enamels. Only one-third of the anatase is used in applications for which its specific properties are highly valued, such as when a bluish tint is desired in some plastics. Anatase is also used because of its photocatalytic properties; total global demand for its use as an active material for the removal of nitrogen oxide compounds from waste gases of coal-fired power plants and for the cleaning of exhaust gases of diesel engines is 15 000 tonnes per year (Linak & Inoguchi, 2005; Swiler, 2005).

Traditionally, the industry has produced a wide variety of grades of titanium dioxide that are tailored for specific applications. In recent years, producers have introduced so-called 'multipurpose products' to try to reduce the number of grades needed in an effort to increase operating efficiency. For example, in the paint market, titanium dioxide manufacturers propose a universal product that is acceptable for use in flat (low-gloss) and enamel (high-gloss) coatings (Linak & Inoguchi, 2005).

Some products with coarse particle sizes are obtained at an intermediate step (before coating with inorganic oxides) in the manufacture of pigmentary titanium dioxide. Manufacturers propose a 'buff' titanium dioxide that is made by grinding rutile ore to yield a product with a 95% titanium dioxide content that can be used as a partial replacement for white titanium dioxide in formulations that are tinted with other colour pigments. Total estimated global production of pigment by this process is about 10 000 tonnes per year (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

Ultrafine grades of titanium dioxide (particle size, 1–150 nm), which transmit visible light but scatter UV radiation, are used as UV blockers in sunscreens and plastics, catalysts and colour pigment precursors and in electroceramics (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

Relatively small quantities of titanium dioxide are used for non-pigmentary purposes. The estimated global market is 110 000 tonnes per year, and the largest user sectors are enamels and ceramics (25–30%), glass and glass ceramics (25–30%), electroceramics (10–15%), catalysts and catalyst supports (10–15%) and welding fluxes (10–15%) (Kischkewitz *et al*., 2002; Linak & Inoguchi, 2005).

1.3   Occurrence and exposure

1.3.1   *Natural occurrence*

Titanium is the ninth most abundant element in the world, it is five times less abundant than iron but 100 times more abundant than copper. The chemical composition

of titanium dioxide is described in detail in Section 1.1.3 and its sources in Section 1.2.1(*a*).

1.3.2   *Occupational exposure*

On the basis of a National Occupational Exposure Survey, conducted in the USA between 1981 and 1983, the National Institute for Occupational Safety and Health (NIOSH, 1983) estimated that 2.7 million workers (2.2 million men and 0.5 million women) were potentially exposed to titanium dioxide. [This estimate is based on a survey of companies and did not involve measurements of actual exposure; for many workers, very low levels and/or incidental exposures to titanium dioxide may be incurred.]

No estimate of the number of workers currently exposed to titanium dioxide was available to the Working Group.

(a)   *Manufacture of titanium dioxide*

The highest levels of exposure within a titanium dioxide manufacturing plant are generally observed in the milling and packing areas (Fryzek *et al*., 2003). In these areas, titanium dioxide is finely processed by micronizers, and dust from the bags used for shipment may be dispersed through the air during bagging by the packers. Lower, but consistent, exposure to titanium dioxide may be incurred by treatment operators, who are involved in the addition of special coatings to and treatments of titanium dioxide before the product is finally milled and packed. Although maintenance mechanics are not exposed to titanium dioxide on a daily basis, they may experience short periods of heavy exposure during routine maintenance and repair activities associated with precipitation of titanium dioxide and subsequent processes or post-oxidation steps. Minimal exposure to titanium dioxide is incurred by workers who are involved in the initial processing and refinement of the product. In addition, general labourers or helpers, laboratory workers who work mainly in the laboratories to monitor the product and workers who handle raw ore also have minimal exposure to titanium dioxide.

Fryzek *et al*. (2003) reported results from 914 personal full-shift or near full-shift air samples for 'total' titanium dioxide that were obtained from four plants between 1976 and 2000 (Table 1.5). Eighteen of these samples appeared to the authors to be unrealistically high and were limited to 50 mg/m^3. The highest exposures were observed for packers, micronizers and workers involved in shovelling spilled titanium dioxide into bags (*n*=686; mean, 6.0 mg/m^3). Exposure levels decreased over time from a mean of 13.7 mg/m^3 (*n*=21) in 1976–80 to 7.9 mg/m^3 (*n*=87) in 1981–85, 6.4 mg/m^3 (*n*=210) in 1986–90, 5.3 mg/m^3 (*n*=239) in 1991–95 and 3.1 mg/m^3 (*n*=357) in 1996–2000.

In seven titanium dioxide manufacturing plants in Europe, Boffetta *et al*. (2003) reported results from 1348 personal exposure measurements of titanium dioxide dust that were predominantly collected during routine measurement programmes. The results related to inhalable, respirable and 'total' dust measurements, which were converted to respirable dust levels using several conversion factors. To convert 'total' to inhalable dust,

a conversion factor of 1.2 was used, based on a study by Kenny *et al*. (1997). A factor of 0.3 was chosen to convert inhalable titanium dioxide dust measurements to respirable measurements, based on results from a study in the European carbon black manufacturing industry (Gardiner *et al*., 1992). Table 1.6 summarizes the results for these standardized levels of respirable titanium dioxide for the packing areas in these plants. The highest levels were observed in Factory 10, where the geometric mean (GM) respirable dust levels ranged from 7.99 mg/m^3 between 1970 and 1974 to approximately 1.3–2.2 mg/m^3 between 1980 and 1999. The authors mentioned that one of the possible reasons for the relatively high exposure levels in Factory 10 may reflect the conversion factors used rather than actual differences in exposure, and care should be taken when interpreting the differences in exposure between the factories.

Although not reported in the study by Boffetta *et al*. (2003, 2004), results from other areas in the titanium dioxide plants were also obtained. Table 1.7 includes results from inhalable and 'total' dust measurements that have been converted to respirable dust levels, and should therefore be interpreted with some care. Highest levels of exposure to respirable dust were found in the drying and milling (GM range, 0.19–2.12 mg/m^3) and packing (GM, 0.48–2.11 mg/m^3) areas, although high exposure levels were also observed for maintenance workers (GM, 0.62–2.24 mg/m^3), handymen (GM, 4.02 mg/m^3) and cleaners (GM, 5.02 mg/m^3). Exposure levels appear to have declined between 1970 and 2000, due to the implementation of control measures such as local exhaust ventilation, increased automation and isolation or segregation of personnel (Sleeuwenhoek, 2005).

To enable a quantitative exposure–response analysis, exposure reconstruction was undertaken for each occupational title at each plant for different time periods (Boffetta *et al*., 2003, 2004) using a method developed by Cherrie *et al*. (1996). The yearly estimated exposure to titanium dioxide dust by factory between 1950 and 1999 varied between 0.1 and 1.0 mg/m^3 (Boffetta *et al*., 2004). However, very high exposure levels were estimated (>7 mg/m^3) in several factories either for cleaning jobs during the end of the production process or for jobs that involved recycling of titanium dioxide dust. Jobs with the highest estimated exposure to titanium dioxide were recycling/blending, sweeper, cleaner, packing, drying, warehouseman and fitter/mechanic (Boffetta *et al*., 2003). The authors observed a decreasing trend in exposure, particularly in factories with the highest estimated exposures during the early production period. Although the highest exposure levels in the factory were in the order of 1.0 mg/m^3, average levels ranged up to 5.0 mg/m^3 for individual occupational titles (Boffetta *et al*., 2004).

Somewhat higher exposure levels were found in earlier studies. Reported concentrations of total dust ranged from 10 to 400 mg/m^3 during the grinding of titanium dioxide pigment, but documentation of these levels was not provided (Elo *et al*., 1972). Long-term exposures to titanium dioxide dust in a titanium pigment production factory occasionally exceeded 10 mg/m^3, and exposures greater than 10 mg/m^3 were common during the repair of production machinery (Rode *et al*., 1981).

Table 1.5. Personal 'total' exposure to titanium dioxide in four titanium dioxide manufacturing plants in the USA by job category (1976–2000)

Job category	No.	Mean (mg/m^3)	SD	Median (mg/m^3)	GM (mg/m^3)
Packers, micronizers and addbacks	686	6.2	9.4	3.0	2.7
Ore handlers	21	1.1	1.1	0.9	0.6
Maintenance mechanics	59	2.5	6.9	0.7	0.7
Dry and wet treatment	117	2.0	7.6	0.3	0.4
Other exposed jobs	31	0.6	0.9	0.4	0.4

Adapted from Fryzek *et al.* (2003)
GM, geometric mean; No., number of samples; SD, standard deviation

Table 1.6. Exposure to titanium dioxide in packing areas in titanium dioxide manufacturing plants in Europe

Factory	Year	No. of measurements	GM (mg/m^3)	Interquartile range	Range
1	1995–99	55	1.33	0.46–3.31	0.10–19.86
	2000–02	9	0.68	0.20–2.74	0.13–4.17
3	1990–94	1	0.25	–	–
	1995–99	61	0.88	0.50–1.90	0.04–7.74
	2000–02	6	0.69	0.27–1.75	0.27–3.83
6	1990–94	6	1.24	0.61–2.47	0.47–5.14
	1995–99	13	2.51	1.63–4.31	0.72–9.72
8	1995–99	11	0.77	0.48–0.96	0.32–6.16
9	1985–89	12	1.57	0.96–2.44	0.72–4.64
	1990–94	16	2.00	1.44–3.08	0.64–3.39
	1995–99	18	1.31	0.80–1.99	0.40–4.24
10	1970–74	10	7.99	3.64–16.64	2.34–79.20
	1975–79	20	2.49	1.64–3.53	1.01–6.41
	1980–84	22	2.16	1.25–3.88	0.63–10.91
	1985–89	18	1.31	0.94–1.93	0.68–5.04
	1990–94	19	1.34	0.94–2.23	0.32–5.29
	1995–99	6	2.11	1.60–3.28	0.47–3.96
15	1985–89	76	0.47	0.31–0.70	0.02–3.54
	1990–94	92	0.45	0.29–0.66	0.06–4.94
	1995–99	37	0.63	0.32–1.57	0.04–4.89

Adapted from Boffetta *et al.* (2003)
GM, geometric mean

Table 1.7. Measurements of respirable dust (mg/m^3) from the white end^a of the titanium dioxide manufacturing process in Europe (1970–2000)

Area	Plant	No.	GM	Interquartile range	Range
Moore filtration	1	8	0.11	0.06–0.54	<0.01–0.94
	8	8	0.28	0.16–0.64	0.08–0.80
Calcination	10	28	0.78	0.36–1.25	0.18–4.79
	15	4	1.01	0.40–3.18	0.39–3.68
Raymond mills and conveying	9	29	1.20	0.88–1.72	0.25–3.84
Surface treatment	1	59	0.66	0.29–1.31	0.05–17.30
	15	5	0.10	0.04–0.37	0.04–0.57
Drying and milling	3	30	0.44	0.12–1.62	0.02–10.80
	8	2	0.71	–	0.48–1.04
	9	46	2.12	1.40–3.82	0.49–7.76
	10	135	1.37	0.86–2.09	0.32–20.66
	15	6	0.19	0.08–0.89	0.02–2.35
Packing	1	64	1.21	0.45–2.97	0.10–19.86
	3	68	0.84	0.46–1.72	0.04–7.74
	6	19	2.01	1.25–4.26	0.47–9.72
	8	11	0.77	0.48–0.96	0.32–6.16
	9	46	1.59	0.96–2.57	0.04–4.64
	10	95	2.11	1.12–3.42	0.32–79.20
	15	205	0.48	0.30–0.70	0.02–4.94
Warehouse	3	38	0.29	0.15–0.53	0.04–4.89
	10	6	1.96	1.32–2.84	1.08–3.28
Forklift truck driver	15	12	0.45	0.24–0.97	0.14–2.14
Loader	15	13	0.29	0.15–0.35	0.10–4.98
Maintenance	1	32	0.62	0.14–1.59	0.04–9.07
	3	28	0.97	0.33–2.79	0.04–18.86
	10	47	2.24	1.30–3.38	0.54–10.19
White end	8	5	1.36	0.60–3.32	0.32–3.44
Handyman	10	44	4.02	2.54–7.35	0.72–20.16
Cleaner	10	9	5.02	3.40–8.71	1.15–9.68

Adapted from Sleeuwenhoek (2005)

GM, geometric mean

^{a} White end, TiO_2 precipitation and all subsequent processes

(b)   Particle concentration

Wake *et al*. (2002) reported the results of measurements taken with a P-trak, Portacount or scanning mobility particle sizer in a titanium dioxide manufacturing plant in the United Kingdom. The particle number concentrations in the bagging area ranged from 4.2×10^3 particles/cm^3 to 16.6×10^3 particles/cm^3 compared with 9.7–58.4×10^3 particles/cm^3 outside the plant on the same day, which indicated that exposure to ultrafine particles (not in conglomerates) is relatively low. [The report does not specify what method was used to count the airborne titanium dioxide particles or what size particles were included in these measurements.]

Various other exposure concentrations have been reported in the manufacture of titanium dioxide, such as ore and other dusts, sulfuric acid, sulfur dioxide, welding fumes, hydrochloric acid and asbestos.

(c)   User industries

Titanium dioxide is used in various industries (see Section 1.2.2) and exposure may occur before and during the addition of titanium dioxide to matrices such as paints, coatings, plastics, rubber, ink and foodstuffs. The potential for exposure is greatly reduced in other parts of the process. Very little information is available on exposure to titanium dioxide in various user industries.

In the pulp, paper and paper product industry, Kauppinen *et al*. (2002) estimated that 70% of stock preparation departments had an exposure prevalence greater than 5% (i.e. more than 5% of the workforce was exposed); this proportion was 73% for on-machine coating of paper. The median level of exposure in these departments was assessed to be between 1.5 and 10 mg/m^3.

No significant exposure to primary particles of titanium dioxide is thought to occur during the use of products in which titanium dioxide is bound to other materials, such as in paints.

1.3.3   *Environmental exposure*

No information was available to the Working Group on environmental exposure to titanium dioxide.

1.4   Regulations and guidelines

Occupational exposure regulations and guidelines in several countries are presented in Table 1.8.

Current occupational exposure limits for titanium dioxide in the USA are based on the airborne mass fractions of either respirable or 'total' dust fractions, and may be the same for titanium dioxide and particles that are not otherwise regulated or classified, with limits ranging from 1.5 mg/m^3 for respirable dust excluding ultrafine particles (Federal Republic

TITANIUM DIOXIDE   211

Table 1.8 Occupational exposure standards and guidelines for titanium dioxide

Country or region	Concentration (mg/m³)	Interpretation
Austria	6	TWA – ACC
Belgium	10	TWA – ACC
China	8 (T)	TWA
	10 (T)	STEL
	0 (T)	Ceiling
Canada		
Alberta	10 (T)	TWA
British Columbia	3 (R)	TWA
	10 (T)	TWA
	20 (T)	STEL
Ontario	10 (T)	TWA
Quebec	10 (T)	TWA; containing no asbestos and < 1% crystalline silica
Czech Republic	10	TWA – ACC
Denmark	6 (as Ti)	TWA
Finland	10	TWA
France	10	TWA
Germany	1.5[a] (R)	MAK (see also aerosol allowable concentrations)
Greece	10	TWA – ACGIH (from ACC)
Hong Kong	3 (R)	TWA
	10 (T)	TWA
Ireland	4 (R)	TWA
	10 (I)	TWA
Italy	10	TWA – ACGIH (from ACC)
Mexico	10	TWA
	20	STEL
Netherlands	10 (I)	TWA – ACC
	5 (R)	TWA – ACC
New Zealand	10 (I)	TWA; containing no asbestos and <1% free silica
Norway	5	TWA
Poland	10 (I)	TWA; containing no asbestos and <2% free crystalline silica
Portugal	10	TWA – ACGIH (from ACC)
South Africa	5 (R)	TWA
	10 (I)	TWA
Spain	10	TWA
Sweden	5 (T)	TWA
Switzerland	3	TWA
United Kingdom	4 (R)	TWA
USA		
ACGIH (TLV)	10 (A4)	TWA
NIOSH (REL)	(Ca)	lowest feasible concentration
OSHA (PEL)	15 (T)	TWA

From Direktoratet for Arbeidstilsynet (2002); SUVA (2003); American Chemistry Council (2003); ACGIH Worldwide (2005); Deutsche Forschungsgemeinschaft (2005); Health and Safety Executive (2005); INRS (2005); Työsuojelusäädöksiä (2005)

A4, not classifiable as a human carcinogen; ACC, American Chemistry Council; ACGIH, American Conference of Government Industrial Hygienists; Ca, potential occupational carcinogen; I, inhalable dust; MAK, maximum concentration at the workplace; NIOSH, National Institute of Occupational Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; R, respirable dust; REL, recommended exposure level; STEL, short-term exposure limit; T, total dust; TLV, threshold limit value; TWA, 8-h time-weighted average

[a] Excluding ultrafine or aggregates of ultrafine

of Germany maximum concentration value in the workplace) to 15 mg/m^3 for total dust (Occupational Safety and Health Administration, 2002). The National Institute for Occupational Safety and Health (NIOSH, 2005) currently has no recommended exposure limit for titanium dioxide in the USA and classifies it as a potential occupational carcinogen. [The Working Group is aware that the National Institute for Occupational Health is considering recommending exposure limits of 1.5 mg/m^3 for fine titanium dioxide and 0.1 mg/m^3 for ultrafine titanium dioxide as time-weighted average concentrations for up to 10 hour per day during a 40-hour work week. This recommendation would remove the current classification of titanium dioxide as an occupational carcinogen.]

1.5   References

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TITANIUM DIOXIDE 213

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2. Studies of Cancer in Humans

Studies on compounds related to titanium dioxide such as titanium tetrachloride or titanium metal dust (Garabrant *et al*., 1987; Fayerweather *et al*., 1992) are not included in this monograph.

2.1   Case report

Yamadori *et al*. (1986) reported a papillary adenocarcinoma of the lung and titanium dioxide-associated pneumoconiosis in a male titanium dioxide packer with 13 years of potential dust exposure and a 40-year history of tobacco smoking.

2.2   Cohort studies (Table 2.1)

Chen and Fayerweather (1988) conducted an industry-based epidemiological study and described mortality and cancer incidence among 1576 male employees who had been exposed to titanium dioxide for more than 1 year in two plants in the USA. Information on cancer incidence was obtained from the company cancer registry, which was started in 1956. Information on deaths among active and retired employees was obtained from the company mortality registry, which was started in 1957. Vital status was determined for about 94% of the cohort, and death certificates were available for about 94% of those known to have died. Observed numbers of incident cases of cancer were compared with expected numbers based on company rates, and the observed numbers of deaths were compared with both company rates and rates in the USA. Mortality from all cancers was lower than expected. For lung cancer, nine deaths were observed, with 17.3 expected on the basis of national rates (standardized mortality ratio (SMR), 0.52 [95% confidence interval (CI), 0.24–0.99]) and 15.3 expected on the basis of company rates (SMR, 0.59 [95% CI, 0.27–1.12]). There was a slight excess of incident cases of cancer (38 observed, 32.6 expected; SMR, 1.17 [95% CI, 0.83–1.60]) due mainly to 10 cases of tumours of the genitourinary system versus 6.3 expected (SMR, 1.59 [95% CI, 0.76–2.92]); eight cases of lung cancer were observed whereas 7.7 were expected (SMR, 1.04 [95% CI, 0.45–2.05]). No increase in mortality from other cancers was observed. [The Working Group noted that details of exposure to titanium dioxide and other factors were not described, that cancer mortality and specific cancer sites were not reported in detail, that incident cases of cancer only in actively employed persons were used for both observed and company reference rates, and that the numbers of incident cases were compared only with company rates.]

In a nested case–control study conducted in a cohort of workers from the oldest and largest of the two plants, no increased risk for lung cancer was found with estimated

Table 2.1. Industry-based studies of titanium dioxide and cancer

Reference, location	Study population	Exposure assessment	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders comments
Chen & Fayerweather (1988); Fayerweather *et al.* (1992), USA	1576 male wage-grade employees in two titanium dioxide production plants who worked for ≥1 year before 1 January 1984; mortality follow-up from 1935 through to 1983; incident cases of cancer in 1956–85 from company insurance records	Committees were established at the plants to estimate exposure to titanium dioxide for all jobs; a cumulative exposure index, duration and time-weighted average were derived and used in the analysis.	Lung cancer Genito-urinary cancers	**Deaths** 9 9 **Cases** 8 **Cases (from case–control study)** 16 10/6.3	0.52 (0.24–0.99) 0.59 (0.27–1.12) 1.04 (0.45–2.05) 0.6 (CI not reported) [1.59 (0.76–2.91)]	Age, exposure to titanium tetrachloride, potassium titanate fibres, asbestos; unclear how the exposure history for controls in the nested case–control study was obtained; unclear if quantitative results from exposure monitoring or sampling were used; adjustment for smoking only made for case–control analyses.
Fryzek *et al.* (2003), USA	Retrospective mortality cohort study of 3832 male and 409 female workers employed for ≥6 months at four titanium dioxide production industries on or after 1 January 1960; follow-up until December 2000	Exposure levels to titanium dioxide assessed by industrial hygienists and based on job history	*All causes* All exposures Packers, micronizers and Addbacks *Trachea, bronchus, lung cancer* All exposures Packers, micronizers and Addbacks *Urinary cancer* All exposures	**Deaths** 533 112 61 11 3	**SMR** 0.8 (0.8–0.9) 0.7 (0.6–0.9) 1.0 (0.8–1.3) 1.0 (0.5–1.7) 0.4 (0.1–1.3)	Sex, age, race, time period, state where the plant was located; not adjusted for smoking; 35% of workers employed in jobs with high potential exposure to titanium dioxide (packers, micronizers, add-backs)

Table 2.1 (contd)

Reference, location	Study population	Exposure assessment	Exposure categories	No. of cases/ deaths	SMR (95% CI)	Adjustment for potential confounders comments
Boffetta *et al.* (2004), Finland, France, Germany, Italy, Norway, United Kingdom	15 017 employees for at least 1 month in production of 11 European titanium dioxide industries (14 331 men); employment started from 1927–69 and ended 1995–2001; mortality follow-up 1950–72 until 1997–2001 (variable per country); 371 813 person–years.	Occupational hygienists reconstructed exposures for each occupational title; exposure estimates were linked with occupational history.	All causes/cancers	**Deaths** *All causes* 2619 men 33 women *All cancers* 807 men 18 women *Lung cancer* 307 men 1 woman	0.87 [0.83–0.90] 0.58 (0.40–0.82) 0.98 (0.91–1.05) 0.96 (0.58–1.54) 1.23 (1.10–1.38) 0.80 (0.02–4.09)	Age/birth cohort, sex, calendar year; women were not included in most analyses (33 deaths only); national rates were used in comparisons.
			Exposure to respirable titanium dioxide dust (mg/m^3)–year *Lung cancer* 0–0.73 0.73–3.43 3.44–13.19 ≥13.20	Men 53 53 52 53	1.0 (reference) 1.19 (0.80–1.77) 1.03 (0.69–1.55) 0.89 (0.58–1.35) (*p* for trend=0.5)	
			Kidney cancer <4.0 4.0–13.9 ≥14		0.45 (0.12–1.16) 1.15 (0.31–2.89) 1.18 (0.37–2.67) (*p* for trend=0.09)	Results for kidney cancer were based on 13 cases among men.

CI, confidence interval; SMR, standardized mortality ratio

exposure to either titanium dioxide or titanium tetrachloride (Fayerweather *et al.*, 1992). [The Working Group noted important methodological limitations of this study, such as a lack of detailed information on exposure assessment, duration of exposure and type of follow-up.]

Fryzek *et al.* (2003) conducted a multicentre study in the USA that included 5713 workers employed on or after 1 January, 1960 for at least 6 months at four titanium dioxide manufacturing plants. Among these, 1472 worked exclusively in administration or in other jobs that did not involve exposure to titanium dioxide. The remaining 4241 workers were followed up until 31 December 2000 (average follow-up, 21 years; standard deviation, 11 years). More workers were employed in chloride plants (53%) than in sulfate plants (40%) and 7% could not be categorized. Nearly 2400 records of air sampling measurements of sulfuric acid mist, sulfur dioxide, hydrogen sulfide, hydrogen chloride, chlorine, titanium tetrachloride and titanium dioxide were obtained from the four plants. Most were area samples and many were of short duration. Exposure assessment was conducted by industrial hygienists with expertise in historical exposure reconstruction. A combination of walk-through surveys, interviews with knowledgeable long-term employees and historical industrial hygiene measurements taken at the plants were used to assign exposure levels to study subjects based on their job history. Only the long-term area samples for total titanium dioxide dust were used. Exposure categories (defined by plant, job title and calendar years in the job) were created to examine mortality patterns for those jobs in which the potential for exposure to titanium dioxide was greatest. Exposure variables representing average exposure per year, years exposed and cumulative exposure were created for titanium dioxide and subjects were categorized into low, medium and high categories of exposure. A total of 914 full-shift or near full-shift personal samples for total titanium dioxide dust were used to estimate relative exposure concentrations between jobs over time (see Table 1.5). The number of expected deaths was based on mortality rates by sex, age, race, time period and the state in which the plant was located. Cox proportional hazard models that adjusted for the effects of age, sex, geographical area and date of first employment were used to estimate relative risks of exposure to titanium dioxide (i.e. average intensity, duration and cumulative exposure) in medium- or high-exposure groups versus the lowest exposure group. SMRs were calculated for all workers as well as separately by type of plant (sulfate and chloride). Information on vital status was found for 4194 of the 4241 (99%) workers in the study cohort. Of the 4241 workers (58% white, 90% male), 958 did not have adequate information on work history and were omitted from some plant analyses. Of the 533 deceased workers, information on cause of death was found for 511 (96%). Thirty-five per cent of the workforce had worked in one of the jobs with the highest potential exposure to titanium dioxide, i.e. packing, micronizing or internal recycling. Information on tobacco smoking was abstracted from medical records for 2503 workers across all four plants from 1960 onwards, but no individual adjustments were possible. It was stated that SMRs for women did not differ appreciably from those for men and only analyses for both sexes combined were presented. The SMR for all causes of death was significantly

lower than expected (SMR, 0.8; 95% CI, 0.8–0.9); the SMR for all causes of death for sulfate plants was higher (SMR, 0.9; 95% CI, 0.8–1.0) than that for chloride plants (SMR, 0.6; 95% CI, 0.5–0.7). The number of lung cancers was close to that expected (SMR, 1.0; 95% CI, 0.8–1.3), with little variation by type of plant (sulfate plant: SMR, 1.1; 95% CI, 0.7–1.6; chloride plant: SMR, 0.9; 95% CI, 0.6–1.3). No significant increases were seen for any cause of death by type of plant, and no trends with exposure were observed. Workers with the highest exposure to titanium dioxide (packing, micronizing or internal recycling workers) had a similar pattern of mortality, i.e. significantly smaller number of deaths than that expected for all causes with no excess for lung cancer. No trend of increasing SMRs for malignant or non-malignant lung disease with increasing duration of employment was evident. Internal analyses showed that relative risks for mortality from all causes and mortality due to lung cancer and non-malignant respiratory disease decreased with increasing cumulative exposure. [This cohort was relatively young (about half were born after 1940) making the duration of exposure to titanium dioxide and the latency period for the development of lung cancer rather short. Moreover, the oldest company reports were not available for the authors to evaluate.]

In response to a letter by Beaumont *et al*. (2004), Fryzek *et al*. (2003) indicated no significant exposure–response relationships for mortality from lung cancer and cumulative exposure to titanium dioxide (i.e. 'low', 'medium' and 'high') with either a time-independent or a time-dependent exposure variable and a 15-year exposure lag (adjusted for age, sex, geographical area and date of first employment).

Boffetta *et al*. (2004) studied mortality from lung cancer among workers employed in 11 plants that produced titanium dioxide in six European countries (Finland, France, Germany, Italy, Norway and the United Kingdom). Overall, 27 522 titanium dioxide-exposed workers first employed between 1927 and 2001 were identified. Workers who were first employed after 1990, employed for less than 1 year in total or who worked in non-production jobs were excluded from analyses, which left a total of 15 017 workers (14 359 men and 686 women). Of the 11 plants, seven had only produced titanium dioxide using the sulfate process and two had only produced titanium dioxide using the chloride process. One plant operated both sulfate and chloride processes and the other plant that currently used the sulfate process had operated a chloride process for a short period. Follow-up for mortality was conducted in all countries and ranged from 27 years in Italy (1972–99) to 47 years in the United Kingdom (1954–2001). A total of 3.3% of cohort members were lost to follow-up and 0.7% had emigrated. The cause of death was unknown for 5.9% of deceased cohort members. Two occupational hygienists performed a comprehensive assessment of exposure, which was carried out at the level of occupational title for each plant for discrete time periods throughout the history of plant operations. Exposures to respirable titanium dioxide dust, sulfuric acid mist, hydrochloric acid, asbestos and welding fumes were assessed and indices of cumulative exposure were calculated by combining estimates across the entire occupational history of a worker. Exposure reconstruction was based on personal sample measurements that were mainly collected during the 1990s (see Section 1.3). Two factories had measurements from the

late 1980s onwards and one factory had measurements from 1990 onwards. Information on tobacco smoking status was collected for 37.6% of workers included in the analyses. During the period of follow-up, 2619 male and 33 female deaths occurred. The SMR for all causes of death was significantly decreased in both genders: 0.87 [95% CI, 0.83–0.90] among men and 0.58 (95% CI, 0.40–0.82) among women. The country-specific SMR for all causes of death in men ranged from 0.81 in Finland to 0.97 in France. The number of deaths due to all malignant neoplasms was similar to that expected (SMR, 0.98; 95% CI, 0.91–1.05). The only cause of death with a statistically significant increased SMR was lung cancer (SMR, 1.23; 95% CI, 1.10–1.38), based on a fixed-effects statistical model. The SMRs varied from 0.76 (95% CI, 0.39–1.32) in Finland to 1.51 (95% CI, 1.26–1.79) in Germany. Because the heterogeneity between countries was of borderline significance (*p*-value=0.05), a random-effects model was also fitted and gave an SMR of 1.19 (95% CI, 0.96–1.48). There was no evidence of a significant difference in the SMRs for lung cancer according to job titles, or between the sulfate process (including no difference between the black and white ends) and the chloride process. Death rates from lung cancer did not increase with cumulative exposure to titanium dioxide dusts or with duration of employment in titanium dioxide manufacturing plants. In addition, many of the regions where the factories were located had a higher death rate from lung cancer than the national rate for their country, which implied that the SMR for lung cancer would have been lower if regional reference mortality had been used. The analysis of tobacco smoking was limited by the relatively small proportion of workers with known habits mainly during the recent period of follow-up but suggested that, for all countries other than France and the United Kingdom, titanium dioxide workers had a higher prevalence of smoking than the respective national populations. Mortality from lung cancer was not associated with exposure to sulfuric acid mist, asbestos or welding rod fumes in the factory workplace. A positive, non-significant dose–response relationship was suggested between estimated cumulative exposure to titanium dioxide dust and mortality from kidney cancer. No increase was found for this neoplasm in the SMR analysis: the SMRs for the three categories of estimated cumulative exposure to titanium dioxide dust were 0.45 (95% CI, 0.12–1.16), 1.15 (95% CI, 0.31–2.89) and 1.18 (95% CI, 0.37–2.67). Four deaths from pleural cancer were observed, one of which occurred in a worker with only 2 years of employment in the titanium dioxide production industry. Job information was totally lacking for one case and largely lacking for another; however, the remaining jobs in which these workers were employed did not obviously entail exposure to asbestos, although it should be noted that asbestosis was mentioned on the death certificate of one of them. Mortality from pleural cancer in this cohort did not seem to be increased compared with national rates. [Among the strengths of the European titanium dioxide study are the large size, the high follow-up rate and the detailed exposure assessment. The availability of data on tobacco smoking, although limited to slightly more than one-third of the cohort, provided some reassurance that tobacco smoking was unlikely to be a confounder. Besides the lack of adjustment for smoking, other limitations are possible exposure misclassification, which might have biased the results towards the null, the

exclusion of part of the early experience of the cohort from the analysis, which reduces the power of the study to detect an association, and the relatively recent beginning of operation of some of the factories that resulted in a follow-up period that was too short to allow the detection of an increase in risk for lung cancer.]

2.3   Community-based case–control studies (Table 2.2)

Siemiatycki (1991) conducted a hypothesis-generating case–control study in Montréal, Canada, that has been described in detail in the monograph on carbon black. More than 4000 subjects were interviewed and included patients with 20 different types of cancer and a series of population controls. A panel of industrial hygienists reviewed each job history reported by study subjects and assessed exposure to 293 substances. Results on associations between titanium dioxide and several sites of cancer were reported. Some indications of excess risk were found in relation to squamous-cell lung cancer (odds ratio, 1.6; 90% CI, 0.9–3.0; 20 cases) and urinary bladder cancer (odds ratio, 1.7; 90% CI, 1.1–2.6; 28 cases). No excesses were observed for any exposure to titanium dioxide for all lung cancer combined (odds ratio, 1.0; 90% CI, 0.7–1.5; 38 cases), for kidney cancer (odds ratio, 1.1; 90% CI, 0.6–2.1; seven cases) or for cancer at several other sites other than the urinary bladder (odds ratio, 1.7; 90% CI, 1.1–2.6).

Subsequently, Boffetta *et al.* (2001) undertook a new in-depth analysis of the relationship between titanium dioxide and lung cancer in the Montréal study. They included 857 histologically confirmed cases of lung cancer diagnosed during 1979–85 among men aged 35–70 years and a group of controls comprising 533 randomly selected healthy residents and 533 cases of cancer of organs other than the lung. In preparation for the new analysis, the industrial hygienists reviewed and modified some of the attributions of exposure to titanium dioxide. The analysis also used a slightly different categorization for considering subjects as exposed to titanium dioxide. Exposure was classified as 'substantial' when it occurred for more than 5 years at a medium or high frequency and level. Most workers who were classified as exposed to titanium dioxide were painters and motor vehicle mechanics and repairers with painting experience; the highly exposed cases mixed raw materials for the manufacture of paints and plastics that contained titanium dioxide. [The Working Group noted that exposure to paints that contain titanium dioxide may not entail exposure to titanium dioxide particles.] Thirty-three cases and 43 controls were classified as having been exposed to titanium dioxide, for which the odds ratio was 0.9 (95% CI, 0.5–1.5). Results of unconditional logistic models were adjusted for age, socioeconomic status, ethnicity, respondent status (i.e. self or proxy), tobacco smoking, asbestos and exposure to benzo[*a*]pyrene. No trend was apparent according to the estimated frequency, level or duration of exposure for which the odds ratio was 1.0 (95% CI, 0.3–2.7) for medium or high exposure for at least 5 years. Few subjects were classified as exposed to titanium dioxide fumes or to other titanium compounds, but the risk for lung cancer was non-significantly increased for exposure to these agents. Results did not depend on the choice of control group and no significant

Table 2.2. Community-based case–control studies of titanium dioxide and cancer

Reference, study location, period	Characteristics of cases and controls	Exposure assessment	Exposure categories	Exposed cases	Odds ratio (90% CI)	Adjustment for potential confounders and comments
Siemiatycki (1991), Canada, 1979–86	Urinary bladder, lung, squamous-cell lung; 3730 histologically confirmed cases of 20 different cancer types diagnosed from September 1979 to June 1985 in men aged 35–70 years; 533 randomly selected healthy residents and 533 cancer controls not matched	Industrial hygienists/ chemists evaluated occupational histories to estimate exposure	*Occupational exposure*	*Urinary bladder cancer*		Age, family income, ethnicity, respondent (self/proxy), smoking, coffee consumption; hypothesis-generating study (293 exposures were evaluated); substantial exposure was defined as ≥10 years in the industry or occupation up to 5 years before onset
			Any	28	1.7 (1.1–2.6)	
			Substantial	3	4.5 (0.9–22.0)	
				Lung cancer		
			Any	38	1.0 (0.7–1.5)	
			Substantial	5	2.0 (0.6–7.4)	
				Squamous-cell lung cancer		
			Any	20	1.6 (0.9–3.0)	
			Substantial	2	1.3 (0.2–9.8)	
Boffetta *et al.* (2001), Canada	Lung cancer; 857 incident cases from 1979 to 1985; men aged 35–70 years; 533 randomly selected healthy residents and 533 cancer controls not matched	Industrial hygienists based on occupational histories collected by Siemiatycki (1991)			**Odds ratio (95%CI)**	Age, family income, ethnicity, respondent (self/proxy), smoking
			Exposure group			
			Unexposed	821	1.0	
			Ever exposed	33	0.9 (0.5–1.5)	
			Non-substantial exposure	25	0.9 (0.5–1.5)	
			Substantial exposure[a]	8	1.0 (0.3–2.7)	
			Level of exposure			
			Low	25	0.9 (0.5–1.7)	
			Medium	6	1.0 (0.3–3.3)	
			High	2	0.3 (0.07–1.9)	
			Duration of exposure			
			1–21 years	17	1.0 (0.5–2.0)	
			≥22 years	16	0.8 (0.4–1.6)	

CI, confidence interval

[a] Substantial exposure: medium or high level frequency ≥5% for at least 5 years, occurring at least 5 years before the interview.

associations were found with exposure to titanium dioxide and histological type of lung cancer. [The main limitations of this study are the reliance on self-reported occupational histories and expert opinion rather than measurement of exposure. A strength of this study was the availability of lifetime smoking histories and other covariates.]

2.4   References

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3. Studies of Cancer in Experimental Animals

The Working Group identified an issue that relates to the interpretation of several of the inhalation and intratracheal instillation studies of titanium dioxide. A lesion that is frequently seen in rats that have been exposed by inhalation to a range of poorly soluble particles such as titanium dioxide has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell tumour'. Various authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al*., 1993; Carlton, 1994; Mauderly *et al*., 1994; Boorman & Seely, 1995; Rittinghausen *et al*., 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain.

3.1   Oral administration

3.1.1   *Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice, 5 weeks of age, were fed diets containing 0, 2.5 or 5% titanium dioxide (size unspecified; anatase; purity, ≥98%) daily for 103 weeks. Mice were killed at 109 weeks of age, at which time no significant difference in survival was observed between treated and control males (32, 40 and 40 surviving animals in the control, low-dose and high-dose groups, respectively). In females, a dose-related trend in decreased survival was noted (P=0.001, Tarone test; 45, 39 and 33 survivors, respectively). No significant differences in body weights or incidence of tumours were observed between treated and control groups (National Cancer Institute, 1979).

3.1.2   *Rat*

Groups of 50 male and 50 female Fischer rats, 9 weeks of age, were fed diets containing 0, 2.5 or 5% titanium dioxide (size unspecified; anatase; purity, ≥98%) daily for 103 weeks. The rats were killed at 113 weeks of age, at which time no significant difference in survival was observed between treated and control groups of either sex (31, 37 and 36 surviving males and 36, 36 and 34 surviving females in the control, low-dose and high-dose groups, respectively). No significant differences in body weights or incidence of tumours were observed between treated and control groups (National Cancer Institute, 1979).

Groups of 50 male and 50 female Fischer 344 rats, 6 weeks of age, were fed diets containing 0, 1.0, 2.0 or 5.0% titanium dioxide-coated mica (flat platelets; longest

dimension, 10–35 μm; 28% titanium dioxide; 72% mica) for up to 130 weeks. There was no evidence of a carcinogenic effect (Bernard *et al*., 1990).

3.2   Inhalation exposure

3.2.1   *Mouse*

A group of 80 female Crl:NMRI BR mice, 7 weeks of age, was exposed by inhalation to ultrafine titanium dioxide (P25, Degussa, Germany; MMAD, 0.80 μm) for 18 hour per day on 5 days per week for up to 13.5 months (7.2 mg/m^3 for the first 4 months, then 14.8 mg/m^3 for 4 months and 9.4 mg/m^3 for 5.5 months) and then maintained in clean air for a further 9.5 months. A control group of 80 animals was maintained in clean air. The mortality rate was 50% in the titanium dioxide-treated group after 17 months versus 20% in the control group. After 23 months, the percentages of mice with adenomas/adenocarcinomas were 11.3%/2.5% in the titanium dioxide-treated group and 25%/15.4% in the controls. The lung tumour rate in the mice was not significantly influenced by exposure to titanium dioxide (according to the method of Hoel & Walburg) (Heinrich *et al*., 1995).

3.2.2   *Rat*

Groups of 50 male and 50 female Sprague-Dawley rats, 8 weeks of age, were exposed by inhalation to 0 or 15.95 mg/m^3 titanium dioxide (99.9% <0.5 μm; purity unspecified) for 6 hour per day on 5 days per week for 12 weeks. The rats were killed at 140 weeks. Average survival was 116 and 113 weeks for control and treated males, and 114 and 120 weeks for control and treated females, respectively. At the end of the study, 39 and 44 control and treated males and 45 and 45 control and treated females, respectively, were still alive. No significant differences in body weights or incidence of tumours were observed (lung and other respiratory tract tumours were benign; other neoplasms seen in the lung were metastases from tumours of other sites) between treated and control groups (Thyssen *et al*., 1978). [The Working Group noted the short duration of exposure.]

Groups of 100 male and 100 female CD rats, 5 weeks of age, were exposed by inhalation to 0, 10, 50 or 250 mg/m^3 titanium dioxide (rutile; 99% pure; MMAD, 1.5–1.7 μm; ~84% of dust particles <13 μm) for 6 hour per day on 5 days per week for 2 years, at which time all surviving rats were killed. No differences in mortality, body weights or clinical signs were observed. The incidence of lung tumours was increased in both male and female high-dose rats (adenomas: 2/79, 1/71, 1/75 and 12/77 (*P*<0.001) control, low-, mid- and high-dose males, respectively; 0/77, 0/75, 0/74 and 13/74 (*P*<0.001) females, respectively; squamous-cell carcinomas: 0/79, 0/71, 0/75 and 1/77 males and 0/77, 1/75, 0/74 and 13/74 (*P*<0.001) females, respectively). One anaplastic carcinoma occurred in a low-dose male (Lee *et al*., 1985a,b, 1986). Difficulty

was experienced in distinguishing between keratinizing squamous metaplasia and squamous-cell carcinomas (Trochimowicz *et al*., 1988). The 15 squamous-cell carcinomas reported (Lee *et al*., 1985a,b; 1986; Trochimowicz *et al*., 1988) were re-evaluated by Warheit and Frame (2006), who described 11 of the squamous-cell carcinomas as non-neoplastic pulmonary keratinizing cysts.

Groups of 50 male and 50 female SPF Fischer 344 rats, 8 weeks of age, were exposed to titanium dioxide (5.0 ± 0.7 mg/m^3; 99.5% rutile; MMAD, 1.1 μm) for 6 hour per day on 5 days per week or air only (control) for 24 months then maintained in clean air for a further 1.5 months. No treatment-related effects on lifespan or causes of death were observed. No differences in tumour development were seen between the groups (one adenoma and one adenocarcinoma in treated animals and two adenomas and one adenocarcinoma in controls) (Muhle *et al*., 1989, 1995). [The Working Group noted the relatively low exposure concentration.]

A group of 100 female Wistar rats, 7 weeks of age, was exposed by inhalation to titanium dioxide (P25, Degussa, Germany; MMAD, 0.80 μm) for 18 hour per day on 5 days per week for up to 24 months (7.2 mg/m^3 for the first 4 months, then 14.8 mg/m^3 for 4 months and 9.4 mg/m^3 for 16 months) and then maintained in clean air for a further 6 months. A control group of 220 animals was maintained in clean air. After 30 months, 32/100 treated rats had lung tumours (20 benign squamous-cell tumours, three squamous-cell carcinomas, four adenomas and 13 adenocarcinomas) in contrast to only 1/217 controls (one adenocarcinoma). Lung tumour incidence was 19/100 when benign squamous-cell tumours were not included (Heinrich *et al*., 1995).

3.3   Intratracheal administration

3.3.1   *Mouse*

Groups of 24 and 22 female A/J mice, 20 weeks of age, received a single intratracheal instillation of a suspension of 0.5 mg titanium dioxide (>99.9% pure; size unspecified) in saline or saline alone (control), respectively, and were maintained until 105 weeks of age. No differences in the incidence of lung tumours (17/24 versus 19/22 controls) or tumour multiplicity (2.24 ± 1.35 versus 1.42 ± 0.77) were noted (Koizumi *et al*., 1993). [The Working Group noted the single administration of a low dose.]

3.3.2   *Rat*

Groups of 24 or 48 female SPF Wistar (HsdCpb:WU) rats, 8–9 weeks of age, received weekly intratracheal instillations under carbon dioxide anaesthesia of one of three types of titanium dioxide. The first type was P25: hydrophilic, majority anatase; mean particle size, ~0.025 μm; density, 3.8 g/mL; specific surface area, 52 m^2/g. The second type was P805 (AL 90 003-2): hydrophobic; mean particle size, 0.021 μm [data on T805 were available to the authors and the Working Group assumed that T805 was

TITANIUM DIOXIDE   227

very similar to P805]; density, 3.8 g/mL; specific surface area, 32.5 m^2/g. The third type was AL 23 203-3: hydrophilic, anatase; mean particle size, ~0.2 μm; density, 3.9 g/mL; specific surface area, 9.9 m^2/g. The dusts were suspended by ultrasonification in 0.4 mL 0.9% phosphate buffered sodium chloride solution, and Tween 80® was added (1.0%) as a detergent to improve the homogeneity of the dosed suspensions. A control group was maintained untreated. Table 3.1 summarizes the experimental groups and the doses instilled. Rats were inspected for clinical signs of morbidity and mortality twice per weekday and once a day on weekends. The experiment was terminated at 30 months unless rats were killed when moribund or diagnosed with a growing subcutaneous tumour. Because of acute toxicity, the number of animals exposed to the hydrophobic titanium dioxide was reduced. After death of the animals and before necropsy of the thoracic and abdominal cavity, lungs were insufflated *in situ* with formalin via the trachea. In particular, the surface of the lung was inspected and lesions were recorded. Lungs were embedded in paraffin and sections were stained with haematoxylin-eosin. All suspected tumour tissues that were taken from other sites were also examined for histopathological lesions, especially for tumours that might be primary tumours with lung metastases. Table 3.1 also summarizes the lung tumour incidence of each group. Statistically significant increases in benign and/or malignant lung tumours were observed with both types of hydrophilic titanium dioxide (Pott & Roller, 2005).

Table 3.1. Dose schedules and incidence of tumours in female SPF Wister rats after intratracheal instillation of titanium dioxide

Type of titanium dioxide	Dose instilled	No. of rats at start/at risk[a]	50% survival (weeks)[b]	Lungs with benign tumours[c] (%)	Lungs with malignant tumours[c] (%)	Lungs with total tumours[c] (%)	Lungs with metastases of other tumours (%)
P25, hydrophilic	5×3 mg	48/42	114	21.4	31.0	52.4	14.3
	5×6 mg	48/46	114	17.4	50.0	67.4	15.2
	10×6 mg	48/46	104	23.9	45.7	69.6	15.2
P805, AL90, hydrophobic	15×0.5 mg[d]	24/11	86	0.0	0.0	0.0	9.1
	30×0.5 mg[d]	48/15	114	6.7	0.0	6.7	6.7
AL23, anatase, hydrophilic	10×6 mg	48/44	108	15.9	13.6	29.5	11.4
	20×6 mg	48/44	113	38.6	25.0	63.6	2.3
No treatment	–	48/46	113	0.0	0.0	0.0	13.0

From Pott & Roller (2005)
[a] Number of rats examined that survived at least 26 weeks after the first instillation.
[b] Period after first instillation in which 50% of the animals died excluding rats that died immediately after anaesthesia.
[c] Primary lung tumour types diagnosed; benign: adenoma, epithelioma; malignant: adenocarcinoma, squamous-cell carcinoma; lungs with one or more malignant tumours may additionally have had benign tumours.
[d] The doses had to be reduced because of unexpected acute toxicity.

3.3.3   *Hamster*

Groups of 24 male and 24 female Syrian golden hamsters, 6–7 weeks of age, received intratracheal instillations of 0 (control) or 3 mg titanium dioxide ([purity unspecified]; particle size: 97% <5 μm; 51% <0.5 μm) in 0.2 mL saline once a week for 15 weeks. The animals were observed until spontaneous death. All control and treated hamsters died by weeks 110–120 and 70–80, respectively, after the beginning of the experiment. The respiratory tract and other organs with gross lesions were examined histopathologically. No respiratory tract tumours were found in the treated groups compared with two tracheal papillomas that were found in untreated controls (Stenbäck *et al*., 1976).

3.4   Subcutaneous injection

Rat

Groups of 20 male and 20 female Sprague-Dawley rats, 13 weeks of age, received a single subcutaneous injection into the flank of 1 mL saline (control) or 30 mg of one of three preparations of titanium dioxide (>99% pure, coated with antimony trioxide; >95% pure, coated with aluminium oxide; or >85% pure, coated with both compounds) in 1 mL saline. All rats were observed until spontaneous death, which occurred as late as 136, 126, 146 and 133 weeks in the control and three titanium dioxide-treated groups, respectively. No tumour was observed at the site of the injection in any group (Maltoni *et al.,* 1982). [The Working Group noted the inadequate reporting of the study.]

3.5   Intraperitoneal injection

3.5.1   *Mouse*

Groups of 30 or 32 male Marsh-Buffalo mice, 5–6 months of age, received a single intraperitoneal injection of 0 (control) or 25 mg titanium dioxide (purity, >98%; manually ground) in 0.25 mL saline, respectively. All survivors (10 control and 13 treated mice) were killed 18 months after treatment. No difference in the incidence of local or distant tumours was observed between treated and control animals (Bischoff & Bryson, 1982).

3.5.2   *Rat*

As part of a large study on various dusts, three groups of female Wistar rats [initial numbers unspecified] (9, 4 and 5 weeks of age, respectively) received intraperitoneal injections of titanium dioxide (P25, Degussa, Germany) in 2 mL 0.9% saline solution. The first group received a total dose of 90 mg/animal in five weekly injections; the second group received a single injection of 5 mg/animal; and the third group received three weekly injections of 2, 4 and 4 mg/animal. One concurrent group of Wistar rats (controls), 5 weeks of age, received a single injection of saline alone. Average lifespans

were 120, 102, 130 and 120 weeks, respectively. No intra-abdominal tumour was reported in 47 and 32 rats that were examined in the second and third groups; six of 113 rats (5.3%) examined in the first group had sarcomas, mesotheliomas or carcinomas of the abdominal cavity [numbers unspecified]. Two of 32 controls (6.3%) had abdominal tumours [tumour type not specified]. In a similar experiment with female Sprague-Dawley rats that received single intraperitoneal injections of 5 mg/animal titanium dioxide, 2/52 rats (3.8%) developed abdominal tumours [tumour type not specified] (average lifespan, 99 weeks). [Controls were not available for comparison in this last experiment] (Pott *et al*., 1987). [The Working Group noted the limited reporting of the study.]

Groups of female Fischer 344/Jslc rats [*n*=330; number of rats per group unspecified], 5 weeks of age, received intraperitoneal injections of one of several man-made mineral fibres, including titanium oxide (rutile) whiskers [fibre length, ~2.5 µm; fibre diameter, ~0.125 µm (estimated from a figure)]. The fibres were given in doses of 5, 10 or 20 mg with 1 mg of dust suspended in 1 mL saline before injection. The greatest volume administered in a week was 5 mL. The fibre concentration of titanium oxide whiskers was 639×10^3/µg. Two years after administration, peritoneal mesotheliomas were induced by silicon carbide whiskers (fibre concentration, 414×10^3/µg; cumulative incidence, 70–100%) and potassium titanate whiskers (fibre concentration, 594×10^3/µg; cumulative incidence, 20–77%) but not by titanium dioxide whiskers (Adachi *et al*., 2001). [The Working Group noted the inadequate reporting of the study.]

3.6   Administration with known carcinogens

Hamster

Groups of 24 male and 24 female Syrian golden hamsters, 6–7 weeks of age, received intratracheal instillations of 3 mg titanium dioxide ([purity unspecified]; particle size: 97% <5 µm; 51% <0.5 µm) plus 3 mg benzo[*a*]pyrene in 0.2 mL saline or 3 mg benzo[*a*]pyrene alone in saline (controls) once a week for 15 weeks. Animals were observed until spontaneous death; all control and treated hamsters had died by 90–100 and 60–70 weeks, respectively. In the 48 hamsters treated with titanium dioxide plus benzo[*a*]pyrene, tumours [number of tumours per sex unspecified] occurred in the larynx (11 papillomas, five squamous-cell carcinomas), trachea (three papillomas, 14 squamous-cell carcinomas, one adenocarcinoma) and lung (one adenoma, one adenocarcinoma, 15 squamous-cell carcinomas, one anaplastic carcinoma). Two papillomas occurred in the trachea of benzo[*a*]pyrene-treated controls. In the same study, ferric oxide (3 mg) and benzo[*a*]pyrene induced a similar spectrum of tumours to that induced by the combination with titanium dioxide (Stenbäck *et al*., 1976).

230   IARC MONOGRAPHS VOLUME 93

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TITANIUM DIOXIDE   231

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4. Mechanistic and Other Relevant Data

The general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discusssed in the Monograph on carbon black in this volume.

4.1   Humans

4.1.1   *Deposition, retention and clearance*

Humans can be exposed to titanium dioxide via inhalation, ingestion or dermal contact. This section describes several case reports of pulmonary findings in humans exposed to titanium dioxide, a clinical study of absorption of titanium dioxide in the gastrointestinal tract and several studies that examined dermal effects and absorption of titanium dioxide from sunscreens.

The human pulmonary studies of titanium dioxide are largely limited to case reports of one or more highly exposed individuals that detail the location of large amounts of titanium dioxide in the tissues. Interpretation of these studies is complicated by co-exposures to other compounds (e.g. cigarette smoke and silica) and a lack of information regarding the estimated delivered pulmonary doses. Therefore, clearance kinetics following acute and chronic exposure to titanium dioxide are poorly characterized in humans relative to animals.

The autopsy of a 55-year-old man was conducted approximately four years after four years of 'heavy' exposure to titanium dioxide (rutile) (Rode *et al*., 1981). The surface of the lungs showed numerous white deposits (1–2 mm in diameter) beneath the intact pleura. Within the lungs, the same white pigment was found fairly evenly distributed among all lobes. The pigment was mainly distributed around the perivascular tissue, but small amounts were found in alveolar walls and in alveolar macrophages. Lymph nodes also contained large amounts of pigment.

Gylseth *et al*. (1984) reported the case of a 53-year-old nonsmoking male farmer who had a mixed dust pneumoconiosis and a lung tumour. The lobe that contained the tumour was removed and analysed. Mineral dusts were deposited in peribronchial and perivascular areas, within alveolar macrophages in the peripheral lung or as small granular accumulations in the interstitium. Dusty deposits were accompanied by local fibrosis. Of the fibres identified, 63% were rutile fibres (0.76–5.5 µm) and 37% were amphibole asbestos (0.7–9 µm).

Yamadori *et al*. (1986) reported the case of a 53-year-old man with pneumoconiosis due to approximately 13 years of occupational exposure to 'high' concentrations of titanium dioxide. The patient died of lung cancer, which was possibly associated with a 34 pack–year smoking history and not attributed to exposure to titanium dioxide. At

autopsy, about 9–10 years after the exposures to titanium dioxide, particle deposition was found to be diffuse in the lung and particles were typically found in interstitial and alveolar macrophages. Examination of lung tissue in the right upper lobe and right hilar lymph nodes showed deposits of crystalloid substances that had a high titanium content and measured 0.2–0.3 µm by 0.7 µm.

Moran *et al*. (1991) analysed lung sections from three male patients (46–57 years of age) with potential occupational exposure to titanium dioxide. Large quantities of dark granular pigment were found in macrophages in the alveolar spaces and around the bronchioles and blood vessels. X-Ray crystallography showed that the lungs of all the patients contained rutile and silica and that those of two of the patients also contained talc.

Böckmann *et al*. (2000) determined blood levels of titanium dioxide (anatase) following oral ingestion of titanium-dioxide capsules and/or powder in six adult men (24–66 years of age). Titanium dioxide was absorbed by the gastrointestinal tract in a size-dependent manner: smaller particles (0.16 µm) were more readily absorbed than larger ones (0.38 µm). Before the experiment, the background blood levels of titanium dioxide in these men ranged from ~6 to 18 µg/L. Blood levels reached up to ~50 µg/L or 100 µg/L between 4 and 12 hours after intake of 23 mg or 46 mg titanium dioxide, respectively.

In a study of 13 Caucasian skin-surgery patients (four women and nine men aged 59–82 years) who applied a microfine (10–50 nm) titanium-dioxide sunscreen for 9–31 days, Tan *et al*. (1996) found that tissue levels overlapped with those in skin samples collected post-mortem. Furthermore, there was no correlation between duration of sunscreen application and the measured concentrations of titanium dioxide. After 4 days of sunscreen application, Lademann *et al*. (1999) also reported that the deeper layers of the stratum corneum were devoid of titanium dioxide. Pflücker *et al*. (2001) performed tests with three sunscreens that contained different types of titanium dioxide (20 nm, cubic; 100 nm, needles; and 100 nm, needles composed of aggregated 10–15-nm particles). At six hours after application, punch biopsies were taken from each area. Consistent with the in-vitro study by Gamer *et al*. (2006), titanium dioxide pigments were located exclusively on the outermost layer of the stratum corneum in all cases. [The Working Group noted the lack of studies on penetration of titanium dioxide in compromised skin, and that a flex skin model was never used to address this issue.]

4.1.2   *Toxic effects*

None of the case reports provided quantitative industrial hygiene information about the exposure of workers to titanium-dioxide dust.

A small set of studies from the titanium industry where ilmenite (iron titanate) was the dust probably involved in exposure has been reviewed (IARC, 1989).

Many case studies have reported abnormalities related to exposure to titanium. In some, titanium dioxide was still identified in the lungs of workers exposed to respirable titanium dioxide years after exposure had ceased. Some case studies reported varying

degrees of fibrogenic changes to the lung associated with either brief or extended high-level exposures (Elo *et al*., 1972; Määttä & Arstila, 1975). In contrast, others that involved exposure to titanium dioxide pigment materials showed no evidence of lung inflammation or fibrosis (Schmitz-Moormann *et al*., 1964; Rode *et al*., 1981).

Elo *et al*. (1972) reported pulmonary fibrosis or fibrotic changes and alveolar macrophage responses that were identified by thoracotomy or autopsy tissue sampling in three workers who had been employed for 6–9 years in dusty work in a titanium-dioxide factory. No data on workplace exposure were reported. Two workers were 'moderate' or 'heavy' smokers but smoking information was not provided for the third worker. Small amounts of silica were present in all three lung samples and significant amounts of nickel were present in the lung tissue of the autopsied case. Exposure was confirmed using sputum samples that contained macrophages with high concentrations of titanium 2–3 years after their last exposure (Määttä & Arstila, 1975). Titanium particles were identified in the lymph nodes of the autopsied case. The lung concentrations of titanium were higher than those of control autopsy specimens from patients who had not been exposed to titanium dioxide.

A case of granulomatous lung disease was reported in a worker who had possibly been exposed to titanium dioxide at an aluminium smelting plant where he had worked near a firebrick furnace. A lymphocyte transformation test showed a proliferative response to titanium chloride but not to any other metal tested, which suggested a possible link with titanium hypersensitivity (Redline *et al*., 1986).

Yamadori *et al*. (1986) reported titanium dioxide-associated pneumoconiosis in a male titanium-dioxide packer with 13 years of potential dust exposure and a 40-year history of smoking.

In a cross-sectional study of 209 titanium metal production workers, 78 of whom were involved in the reduction process and were exposed to titanium-tetrachloride vapour, titanium oxychloride and titanium-dioxide particles had reductions in lung function (Garabrant *et al*., 1987). The authors noted that this finding could be due to exposure to titanium tetrachloride, which reacts violently with water to liberate heat and produce hydrochloric acid, titanium oxychloride and titanium dioxide. Pleural disease with plaques and pleural thickening was observed in 36 of the 209 workers, including eight of the 78 reduction-process workers. Some cases were probably caused by previous exposure to asbestos; however, among workers who were not known to have been exposed to asbestos, the risk for pleural disease after more than 10 years of employment was 3.8 times that in workers who had been employed for less than 5 years.

Oleru (1987) studied 67 workers in a small titanium oxide paint factory in Nigeria. Airway symptoms were reported by 50–54%, neurological symptoms by 20–40% and other symptoms by 10–27% of the workers. The symptoms were correlated to exposure and with pulmonary function tests. Twenty-eight cases of restrictive lung impairment were observed. Smoking prevalence was low, but several of the workers were also exposed to cotton dust.

A chest X-ray study of 336 workers at two titanium dioxide-production plants showed 19 cases of pleural abnormalities (thickening or plaques) compared with three cases among 62 unexposed workers at the same plants (Chen & Fayerweather, 1988). The odds ratio for chest X-ray abnormality associated with exposure to titanium dioxide was 1.4, although exposures at the plants included titanium tetrachloride, potassium titanate and asbestos. No lung fibrosis was observed.

Moran *et al*. (1991) reported exposure to titanium dioxide in four men and two women. Diffuse fibrosing interstitial pneumonia and bronchopneumonia were reported in three male patients (a titanium dioxide worker, a painter and a paper mill worker) with deposits of titanium dioxide (rutile) in the lung and smaller amounts of silica deposited in the tissues. Smoking information was not reported.

Keller *et al*. (1995) reported a case of pulmonary alveolar proteinosis (i.e. deposition of proteinaceous and lipid material within the airspaces of the lung) in a worker who had been employed for more than 25 years as a painter, with eight years of experience in spray painting, and who smoked two packs of cigarettes per day until he was hospitalized. Titanium was the major type of metallic particle found in his lung tissues.

4.2 Experimental systems

4.2.1 *Deposition, retention and clearance*

A considerable number of toxicological studies, both *in vivo* and *in vitro*, have characterized the disposition (deposition, absorption, distribution and elimination) of titanium dioxide particles in the respiratory tract of animals and cells. Experimental protocols and findings of many of these studies are provided in Tables 4.1–4.3.

Most animal studies on the effects of titanium dioxide on the respiratory tract have been conducted in rats. Generalizations with regard to the effects of inhaled particle size on the amount and site of deposition in the lungs and subsequent clearance are applicable to animals as well as humans and can be made but with some caution. A variety of factors other than particle parameters can influence delivered dose, distribution within the lungs and subsequent clearance. These factors complicate comparisons between studies and interspecies extrapolation of observed effects. Hence, some caution must be advised when comparing results among the various studies in Tables 4.1–4.3. For example, Bermudez *et al*. (2002) exposed rats, mice and hamsters to the same particle size, at the same particle concentration, for the same exposure time. However, despite the same study design, similar doses would not necessarily be received between the species. At a concentration of 250 mg/m^3, mice had a larger normalized pulmonary particle burden than rats and hamsters (170, 120 and 114 mg/g dry lung, respectively).

Normalized particle dose (deposited mass per body weight) delivered to the respiratory tract may decrease with increasing animal size. This was the observation of McMahon *et al*. (1975), who compared aerosol (gold particles, 0.78 μm MMAD) deposition in mice, hamsters, rats, rabbits and dogs. Ferin and Morehouse (1980) also

Table 4.1. Inhalation studies of titanium dioxide (TiO₂) disposition and responses in animal models

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Hooded rats of Long-Evans descent (~250 g)	TiO_2, 1.48 μm MMAD (σ_g=3.26); NO_x or $SO_2 + TiO_2$	100 mg/m^3 for 2, 4 or 6 h; after gaseous exposure, aerosol at 15 mg/m^3 for 7 h	About 10 rats in each group killed at 1, 8, 25 and 130 days after exposure	In non-pollutant-exposed rats, about 40% of TiO_2 cleared by 25 days and 80% cleared by 130 days after inhalation; based on a linear association between TiO_2 levels in the trachea and lung burden, authors suggested that particles were removed from the alveoli via the airways by alveolar macrophages. NO_x and SO_2 stimulated clearance at low-exposure levels and suppressed clearance at higher exposure levels.	Ferin & Leach (1975)
Long-Evans and Fischer 344 rats, male (9 weeks)	TiO_2, 1.0 μm MMAD (σ_g=2.3)	14.9 mg/m^3 for 7 h	10 rats killed at 1, 8, 25 and 130 days after exposure	At days 1 and 25 after exposure, TiO_2 content in lung lobes was significantly associated with lobe weight in both rat strains. The distribution of TiO_2 between lobes was similar between strains. Normalized to lung weight, the smaller Fischer 344 rats received a slightly greater total lung burden than the Long-Evans rats (114 versus 105 μg/g lung). Lung clearance between days 1 and 8 was greater in the Long-Evans than in the Fischer 344 rats, although subsequent clearance rates were quite similar between the strains. At 25 days, 55 and 70% retention was observed in Long-Evans and Fischer 344 rats, respectively. Authors suggested that there may be strain differences affecting early alveolar clearance mechanisms.	Ferin & Morehouse (1980)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Long-Evans rats, male (~300 g)	TiO_2 (anatase), 1.0 μm MMAD (σ_g=2.3), aerosol-as-generated and charge-neutralized aerosols	10.8–15.5 mg/m^3	Rats exposed for 7 h; deposition assessed in 40 rats; clearance assessed at 1, 8, and 25 days after exposure (20 rats per time-point)	On average, the deposition efficiency was 79% for charge-neutralized aerosols and 100% for aerosols-as-generated by a Wright dust feeder. The pattern of deposition within the lungs was unaffected by particle charge as indicated by a no-charge-effect on clearance.	Ferin *et al*. (1983)
Long-Evans rats, males (~300 g)	TiO_2 (anatase), 1.0 μm MMAD (σ_g=2.3); TiO_2 (rutile), 0.83 μm MMAD (σ_g=2.02)	16.5±1.7 mg/m^3, 19.3±3.1 mg/m^3	Rats exposed for 7 h; 8–10 rats killed at 1, 8, 27 and 132 days after exposure	Crystal structure had no effect on pulmonary particle clearance (half-times of 51 and 53 days for anatase and rutile, respectively).	Ferin & Oberdörster (1985)
Crl:CD rats	TiO_2 (rutile), 1.5–1.7 μm MMAD	10, 50, 250 mg/m^3	Four exposure groups of 100 male and 100 female rats exposed 6 h/day, 5 days/week up to 2 years; rats killed at 3, 6, 12 and 24 months.	No abnormal clinical signs, body weight changes or excess mortality in any group compared with controls; at 10 mg/m^3, particles were mostly phagocytosed by alveolar macrophages. At 50 mg/m^3, there was marked hyperplasia of alveolar lining cells with some alveoli adjacent to terminal bronchioles exhibiting ciliated cells; macrophages containing dust were aggregated; cellular debris, proteinosis and fibrosis were observed. Lung weights at 250 mg/m^3 were double those of the 10-mg/m^3 and control groups. Dose-related increase in particle number identified in tracheobronchial lymph nodes, cervical lymph nodes, liver and spleen was observed. Animal grooming could have been the source of the observed extrapulmonary particles.	Lee *et al*. (1985a,b, 1986)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Wistar rats, female	TiO_2 (anatase), 4.8 µm MMAD, 15–40-nm primary particles	8.6 mg/m³	6 rats exposed to each aerosol for 7 h/day for 1 year	TiO_2 particles observed mainly in interstitial macrophages of the alveolar walls; these were frequently aggregated in small granulomas. Lesions associated with TiO_2 particle accumulation distributed throughout alveolar region	Takenaka et al. (1986)
PVG rats, male (12 weeks)	TiO_2 (rutile); quartz	10 mg/m³	Exposed 7 h/day, 5 days/week up to 15 weeks; 4 rats per group killed at days 2, 4, 8, 16, 32, 52, and 75; also, groups of 4 killed 62 days after exposure for 32 and 75 days	Macrophages were predominant cell type in lavages of unexposed controls. Macrophage and PMN levels in TiO_2 group remained at control levels for entire exposure period. Total lavage protein relative to TiO_2 was only slightly increased relative to controls.	Donaldson et al. (1988)
Long-Evans rats, male (220–260 g)	TiO_2, 1 µm MMAD (σ_g=1.4) after $CdCl_2$, 0.4–0.5 µm MMAD (σ_g=1.4–1.6) or before $CdCl_2$, 0.5 µm MMAD (σ_g=1.4)	13.3 mg/m³ (TiO_2); 1.5, 5, 5 mg/m³ ($CdCl_2$)	Rats (180 total) exposed nose-only to $CdCl_2$ followed 12 h after by TiO_2 for 6 h or vice versa to assess effect of Cd on particle clearance kinetics; burden of TiO_2 exposure assessed on days 1, 8, 15, 25 and 46	Relative to saline controls, the overall pulmonary clearance of TiO_2 not affected by $CdCl_2$ inhalation; however, 5-mg/m³ exposures to $CdCl_2$ (either before or after TiO_2 inhalation) caused in increase in the amount of TiO_2 found in the lymph nodes relative to control and 1.5 mg/m³ $CdCl_2$ which did not differ. Authors hypothesized that the cytotoxicity of $CdCl_2$ caused a decrease in macrophage clearance and an increase in transport to lymph nodes although changes in epithelial permeability could not be entirely ruled out.	Greenspan et al. (1988)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Rats	TiO_2 (rutile),1.1 µm MMAD (σ_g=1.6), 200–700-nm primary particles; TiO_2 (anatase), 1.0 µm MMAD (σ_g=1.9), 20–40-nm primary particles; carbon black, 1 µm MMAD (σ_g=2), 14-nm primary particles	5 mg/m^3; 1, 4, 16 mg/m^3; 9.8 mg/m^3; 9 mg/m^3	30 h/week for 3 months; 30 h/week for 22.5 months; 95 h/week for 7 months; 95 h/week for 4.5 months	In general, clearance kinetics of polystyrene (3.5-µm spheres, [85]Sr-labelled) appeared to decrease with increasing volume burden of test materials. Despite having a lower volume burden and larger primary particle size, however, the ultrafine TiO_2 (anatase) tended to clear more slowly than carbon black (half-time 788 versus 420 days, respectively). Fine TiO_2 (rutile) caused a modest reduction in clearance relative to control (half-time 94 versus 74 days, respectively).	Muhle *et al.* (1990)
Fischer 344 rats, male and female (4 weeks)	TiO_2 (rutile), 1.0 µm MMAD (σ_g=1.6), 200–700-nm primary particles	5 mg/m^3	Rats (~12 per time-point and outcome) exposed 6 h/day, 5 days/week for up to 24 months; clearance measured from 15–100 days *in vivo* following acute inhalation of tracer aerosols: 3.5 µm [85]Sr-polystyrene and 0.26–0.39 µm [59]FeO_2	Pulmonary clearance rates decreased in unexposed controls during study. Clearance rates in TiO_2-exposed rats were comparable with controls. Lung burden per mass of lung tissue was similar between males and females. At 15 months of TiO_2 exposure, rats had a small but significant decrease in macrophage levels and an increase in PMNs relative to controls. Epithelial permeability was not affected by TiO_2.	Muhle *et al.* (1990) [clearance kinetics, particle sizes]; Bellmann *et al.* (1991) [clearance kinetics]; Muhle *et al.* (1991) [particle sizes, cytology]

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats, male (180–200 g)	TiO$_2$ (anatase), 1.0 µm MMAD (σ_g=2.6)	50 mg/m^3	Rats exposed 6 h/day for 5 days and killed 1, 2, 4 and 9 weeks after exposure	One day after exposure, lung burden was 1.8 mg/lung for TiO$_2$. At 28 days after exposure, retention was 39%. Inhalation caused lesser effects, e.g. permeability and PMN influx, than instillation of similar lung burdens reported earlier (Driscoll et al., 1990).	Driscoll et al. (1991)
Fischer 344 rats (240–260 g)	TiO$_2$ (anatase), 0.78 µm MMAD (σ_g=1.7), 21-nm primary particles; TiO$_2$ (anatase), 0.71 µm MMAD (σ_g=1.9), 250-nm primary particles	23.5±3.2 mg/m^3; 23.0±4.1 mg/m^3	Chamber exposure for 6 h/day, 5 days/week, for up to 12 weeks; rats killed at 4, 8, 12, 41 and 64 weeks; 4 rats per group, except only three in 41-week group	Retention half-times were 501 and 174 days for ultrafine (21 nm) and fine (250 nm) primary particles, respectively. As a percentage of total lung burden, the unlavageable fraction of particles plus particles in the hilar lymph node were also significantly greater for ultrafine than fine primary particles at 12, 41 and 64 weeks. On average, PMN influx due to ultrafines was 43-fold and 22-fold greater than that for fine particles at weeks 8 and 12 of exposure, respectively. By week 64, PMN levels had approached control levels for both aerosols.	Ferin et al. (1992)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats	TiO_2 (anatase), 0.78 µm MMAD (σ_g=1.7), 21-nm primary particles; TiO_2 (anatase), 0.71 µm MMAD (σ_g=1.9), 250-nm primary particles	23.5 ± 2.9 mg/m³; 22.3 ± 4.2 mg/m³; 1.3 ± 0.3 mg/m³	Rats exposed to aerosols (6 h/day, 5 days/week, 12 weeks); subsequently, 4 rats inhaled and 4 rats instilled with tracer aerosol (3.3 µm, [85]Sr-labelled polystyrene); [85]Sr measured *in vivo* for 180 days	Ferin *et al*. (1992) reported pulmonary retention half-times of 501 and 174 days for inhaled aerosol composed of ultrafine (21 nm TiO_2) and fine (250 nm TiO_2) primary particles, respectively. After TiO_2 exposure, inhaled/instilled polystyrene had slow-phase clearance half-times of 66/72 days (control), 117/99 days (250 nm TiO_2), 541/606 days (21 nm TiO_2). Accelerated tracheobronchial clearance was observed when pulmonary clearance was retarded. For both TiO_2 aerosols, the exposure-induced PMN influx appeared related to particle surface area. Ultrafine TiO_2 induced focal interstitial pneumonia and focal alveolitis.	Oberdörster *et al*. (1994, 1997)
Fischer 344 rats (175–225 g)	TiO_2 (anatase) fine (250 nm) and ultrafine (21 nm) particles delivered as aggregates with 1.0–1.2 µm MMAD (σ_g=1.6–2.2)	125 mg/m³	Rats exposed for 2 h via endotracheal tube while anaesthetized and ventilated; rats (6 per time-point) killed at 0, 1, 3 and 7 days after exposure; pattern of deposition evaluated in 3 rats	Pattern of deposition (TiO_2 mass deposited per lobe) was well correlated with lung lobe size (% total lung weight). Immediately after exposure, total lavage protein significantly increased 7-fold and 3-fold in ultrafine and fine TiO_2 exposure groups, respectively, relative to unexposed controls. One day after exposure, protein levels remained increased by 3-fold in ultrafine exposure group. Significant PMN influx occurred in ultrafine exposure group relative to unexposed controls 1 day after exposure. Comparison of responses as a function of primary particle size was confounded by ~40% greater ultrafine than fine particle mass dose 1 day after exposure.	Osier & Oberdörster (1997)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Crl:CDBR rats, male (7–8 weeks)	TiO_2 (rutile),1.7 µm MMAD, 0.25 µm primary particles	5, 50, 250 mg/m^3	Rats exposed 6 h/day, 5 days/week for 4 weeks; killed at 0 h, 1 week, 1, 3 and 6 months after exposure	After exposure to 5, 50, and 250 mg/m^3, lung burdens for TiO_2 were approximately 0.26, 2.7, and 12 mg, respectively. Clearance rates decreased with increasing exposure concentrations; TiO_2 half-times were 68, 110, and 330 days for 5, 50, and 250 mg/m^3, respectively. Number of particles in lymph nodes was increased in the highest exposure group relative to other exposure and control groups. The highest exposure group also had focal hypertrophy and hyperplasia which were associated with aggregates of pigmented macrophages in alveoli and at alveolar duct bifurcations. These focal lesions were evident for the entire follow-up periods. At 3 months after exposure to 250 mg/m^3 TiO_2, chemotaxis of alveolar macrophages was also reduced. Fibrosis was not observed to any significant degree in any groups.	Warheit *et al.* (1997)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Syrian golden hamsters, male and female (4 weeks)	TiO_2 (rutile), 1.1 μm MMAD (σ_g=1.6), 200–700-nm primary particles	40 mg/m^3 for 5 months, then 30 mg/m^3	Animals (~9 per time-point and outcome) exposed 6 h/day, 5 days/week for up to 18 months; clearance measured 15–100 days *in vivo* following acute inhalation of tracer aerosol (3.5 μm ^{85}Sr-polystyrene)	TiO_2-exposed females tended to have slower clearance rates than similarly exposed males. On average, retention half-times in TiO_2-exposed hamsters were significantly reduced relative to controls at 3 months (control, 78 days; TiO_2, 226 days) and more so at 9 months (control, 115 days; TiO_2, 1120 days). However, at 15 months of TiO_2 exposure, clearance was more similar to controls (control, 88 days; TiO_2, 123 days). Intragroup variability in clearance rates was double that reported for rats by Bellmann *et al*. (1991). Authors suggested possible adaptation capability in hamsters.	Creutzenberg *et al*. (1998)
Wistar rats, male (12 weeks)	TiO_2 (rutile), 2.1 μm MMAD (σ_g=2.2)	25, 50 mg/m^3	Rats exposed 7 h/day, 5 days/week for up to 7 months; typically, 6 rats lavaged and 6 used to assess lung burden at each of 6 time-points	At end of exposures, lung burdens were 17 and 24 mg/g dry lung for low and high exposures to TiO_2. Macrophage levels did not change statistically during exposures. Lymph node burdens and PMN levels rapidly increased with TiO_2 exposures. Findings best associated with lung burden in terms of retained particle surface area. Lymph node burdens and PMN levels increased rapidly beyond a 'threshold' lung burden of 200–300 cm^2 particle surface area.	Cullen *et al*. (2000); Tran *et al*. (2000)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats, female (6 weeks); B3C3F$_1$ mice, female (6 weeks); hamsters, female (6 weeks)	TiO$_2$ (rutile), 1.36–1.44 μm MMAD (σ_g=1.50–1.71), 220-nm primary particles	10, 50, 250 mg/m^3	Total of 65 rats, 65 mice and 73 hamsters exposed 6 h/day, 5 days/week, for 13 weeks; animals killed at 0, 4, 13, 26 and 52 (46 for hamsters) weeks after exposure	TiO$_2$ pulmonary retention half-time for the low-, mid- and high-exposure groups, respectively: 100, 324 and 838 days in rats; 50, 417 and 621 days in mice; and <110 days in hamsters. In rats and mice, PMN levels were significantly elevated in mid- and high-exposure groups and gradually decreased after exposure. However, the rate of PMN decline was far more gradual in the high-exposure groups, especially in rats. PMN levels in the high-exposure group of hamsters responded similarly to mid-exposure groups of mice and rats. In high-exposure groups of rats and mice, epithelial permeability remained elevated (>5 times low-exposure groups) up to 52 weeks, with no signs of recovery.	Bermudez *et al.* (2002)
Fischer 344 rats, female (6 weeks); B3C3F1 mice, female (6 weeks); hamsters, female (6 weeks)	TiO$_2$, 1.29– 144 μm MMAD (σ_g=2.46–3.65), 21-nm primary particles	0.5, 2, 10 mg/m^3	Groups of 25 animals per species and time-point; animals exposed 6 h/day, 5 days/week, for 13 weeks and animals killed at 0, 4, 13, 26 and 52 (49 for hamsters) weeks after exposure	TiO$_2$ pulmonary retention half-times for the low-, mid- and high-exposure groups, respectively: 63, 132 and 365 days in rats; 48, 40 and 319 days in mice; and 33, 37 and 39 days in hamsters. In high-exposure groups of mice, epithelial permeability remained elevated (~twice control groups) up to 52 weeks without signs of recovery. Epithelial permeability was 3–4 times the control in high-dose rats through to 4 weeks after exposure, but approached control by 13 weeks. Epithelial permeability was unaffected in all groups of hamsters.	Bermudez *et al.* (2004)

Table 4.1 (contd)

Species, sex (age/weight)	Aerosol characteristics	Exposure concentration	Exposure protocol	Observed effect(s)	Reference
Wistar rats, adult male (250±10 g)	TiO_2, 22 nm CMD (σ_g=1.7), spark generation	0.11 mg/m^3, 7.3×10^6/cm^3	10 rats exposed 1 h via endotracheal tube while anaesthetized and ventilated at constant rate; lungs fixed at 1 or 24 h after exposure	Distributions of particles among lung compartments followed the volume distribution of compartments and did not differ significantly between 1 and 24 h post-inhalation. On average, 79.3±7.6% of particles was on the lumenal side of the airway surfaces, 4.6±2.6% was in epithelial or endothelial cells, 4.8±4.5% was in connective tissues and 11.3±3.9% was within capillaries. Particles within cells were not membrane-bound.	Geiser *et al*. (2005)

CdCl$_2$, cadmium chloride; CMD, count median diameter; MMAD, mass median aerodynamic diameter; NO$_x$; nitrogen oxide; PMN, polymorphonuclear neutrophils; SO$_2$, sulfur dioxide

TITANIUM DIOXIDE

Table 4.2. Instillation studies of titanium dioxide (TiO$_2$) disposition in animal models

Species, sex (age/weight)	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Long-Evans rats (~300 g)	TiO$_2$ (rutile), 0.5, 5 mg/rat; TiO$_2$ (anatase), 0.5, 5 mg/rat	6 male rats per group instilled with each material in 0.2 mL saline; two control groups: non-instilled and saline-instilled; lung lavaged at 24 h after instillation.	No indication that crystal structure affected biological outcomes. High TiO$_2$ doses (5 mg) caused significant PMN influx relative to control and lower TiO$_2$ doses. Small but significant increase in macrophages after 0.5 mg rutile instillation relative to high TiO$_2$ doses (both rutile and anatase).	Ferin & Oberdörster (1985)
BALB/c BYJ mice, male, (7–8 weeks, ~27 g)	TiO$_2$ 1.57 μm MMAD (σ_g=2.3), 11.8 μg/mouse	Mice (3 per group and time-point) instilled with each material in 20 μL phosphate buffered saline and killed at 6 periods between 15 min and 7 days	PMN levels in TiO$_2$ groups did not differ relative to saline controls at 20 h, 3 days or 7 days after instillation. Lung clearance half-time was 19 days for TiO$_2$.	Finch *et al.* (1987)
Fischer 344 rats, male (180–200 g)	TiO$_2$ (anatase, 2.1±1.5 μm), 5, 10, 50, 100 mg/kg bw	5–6 rats per exposure group killed 1, 7, 14 and 28 days after-instillation; 5-mg/kg dose not assessed at day 1	At all but the lowest instilled dose, TiO$_2$ caused increased PMN levels relative to saline controls at all time-points. At 5-mg/kg TiO$_2$, PMN levels were only increased at day 7. At 28 days following 50 mg/kg, TiO$_2$ was found primarily in macrophages located at the alveolar duct levels.	Driscoll *et al.* (1990)

Table 4.2 (contd)

Species, sex (age/weight)	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats, male (240–260 g)	12-nm TiO_2 (rutile), 500 µg/rat; 21-nm TiO_2 (anatase), 65, 107, 200, 500, 1000 µg/rat; 230-nm TiO_2 (rutile), 500 µg/rat; 250-nm TiO_2 (anatase), 500, 1000 µg/rat	3–8 rats per group killed 24 h after exposure	For doses >500 µg, the unlavageable fraction appeared to correlate with instilled number of particles and decreased with increasing particle diameter.	Ferin *et al*. (1992)
Fischer 344 rats, male (~220 g)	12-nm TiO_2 (rutile), 500 µg/rat; 20-nm TiO_2 (anatase), 65, 107, 200, 500, 1000 µg/rat; 220-nm TiO_2 (rutile), 500 µg/rat; 250-nm TiO_2 (anatase), 500, 1000 µg/rat; 20-nm TiO_2 (anatase, serum-coated), 100 µg/rat; 20-nm TiO_2 (anatase, phagocytosed), 104 µg/rat	4–10 rats per group killed 24 h after exposure	Fraction of particles retained in tissues (epithelial cells or interstitium) and protein leakage correlated with surface area of retained particles. Serum coating did not affect inflammatory response or protein leakage. Phagocytosed particles did not access the tissues or induce an inflammatory response.	Oberdörster *et al*. (1992a)

Table 4.2 (contd)

Species, sex (age/weight)	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats, male (175–225 g)	Fine (250 nm) TiO_2 (anatase), 500 µg/rat; ultrafine (21 nm) TiO_2 (anatase), 750 µg/rat	Rats instilled with particles in 0.2 mL saline (6 per time-point) and killed 0, 1, 3 and 7 days after exposure	Significantly increased PMN influx in rats exposed to ultrafine particles via instillation relative to inhalation and unexposed controls at 1, 3 and 7 days after exposure. Rats instilled with fine particles had a significant increase in PMNs relative to unexposed rats 1 day after exposure only. Significantly increased number of macrophages was present 3 and 7 days after ultrafine instillation relative to inhalation and unexposed controls. Comparison of responses as a function of primary particle size was confounded by ~40% greater ultrafine than fine particle mass dose 1 day after exposure.	Osier & Oberdörster (1997)

Table 4.2 (contd)

Species, sex (age/weight)	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Fischer 344 rats, males (10 weeks; TiO_2 only, 211±10 g; endotoxin plus TiO_2, 235±39 g); C57BL/6J mice, male (23.3±1.6 g, TiO_2 only)	Ultrafine (20 nm) TiO_2 (anatase), 31, 125, 500 μg/rat; 6, 25, 100 μg/mouse; fine (250 nm) TiO_2 (anatase), 125, 500, 2000 μg/rat; 25, 100, 400 μg/mouse; endotoxin before ultrafine TiO_2, 70 endotoxin units, 50 μg/rat; endotoxin before fine TiO_2, 70 endotoxin units, 50 μg/rat	TiO_2 exposure only: 3 animals per group killed at 6, 24 and 48 h after instillation; endotoxin plus TiO_2: instilled with TiO_2 30 min after endotoxin inhalation and killed 24 h after instillation	On the basis of instilled particle mass, ultrafine TiO_2 caused far greater PMN influx than fine particles in both rats and mice at all time-points. Expressed as instilled particle surface area, PMN responses to fine and ultrafine TiO_2 appeared to be similar. In endotoxin-primed rats, ultrafine TiO_2 caused a significant amplification of the PMN response relative to ultrafine TiO_2 or endotoxin alone, whereas fine TiO_2 did not elicit a significant response relative to controls.	Oberdörster *et al*. (2000)
Wistar rats, male (370–470 g)	29-nm TiO_2, 125, 500 μg/rat; 250-nm TiO_2, 125, 500 μg/rat	Rats killed 24 h after exposure	Epithelial permeability, epithelial damage and inflammation were increased following 500 μg instillation of ultrafine particles (29-nm TiO_2) but not fine particles (250-nm TiO_2)	Renwick *et al*. (2004)

bw, body weight; MMAD, mass median aerodynamic diameter; PMN, polymorphonuclear neutrophils

TITANIUM DIOXIDE

Table 4.3. In-vitro studies of titanium dioxide (TiO$_2$) disposition

Cells	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Sprague-Dawley alveolar macrophage cell line	TiO$_2$ [size not specified] up to 100 µg/mL	Particles untreated or opsonized with surfactant protein A, artificial bovine surfactant or rat immunoglobulin G	Opsonization with surfactant components resulted in a modest dose-dependent increase in macrophage uptake of particles compared with untreated particles. These 'inert' particles presumably phagocytosed via receptors that require neither activation nor opsonization by airway surface fluid components	Stringer & Kobzik (1996)
Sprague-Dawley rat tracheal explants	21-nm TiO$_2$ (anatase), 120-nm TiO$_2$ (anatase); 5 mg/mL suspension	Explants submerged epithelial side up; after 1 h, explants removed from suspension and placed in media for 3–7 days	Ultrafine particles appeared to enter epithelial cells more rapidly than fine particles. Results suggested that once ultrafine TiO$_2$ particles enter epithelial cells they are readily translocated to the interstitium, whereas fine particles tend to remain in the epithelial cells. Both fine and ultrafine particles tended to aggregate, but the aggregates of ultrafine particles were larger and encompassed a greater number of particles. The aggregate size of fine particles decreased over time, while that of ultrafine particle increased over time.	Churg et al. (1998)
BALB/C mouse tumour monocytic macrophages, J774.2 cell line	29-nm TiO$_2$, 250-nm TiO$_2$, 15.7–125 µg/mL (0.0975–0.78 µg/mm^2)	Cells cultured for 8 h with particles; medium subsequently changed and cells incubated for 24 h with 2-µm latex beads (5:1, bead:cell) to assess phagocytic activity	Phagocytosis was inhibited by all particle types at 125 µg/mL (0.78 µg/mm^2). However, at the lowest dose (0.0975 µg/mm^2) there was a tendency for ultrafine particles to increase phagocytic activity.	Renwick et al. (2001)

Table 4.3 (contd)

Cells	Characteristics of particles and exposure	Exposure protocol	Observed effect(s)	Reference
Wistar rat lung macrophages	29-nm TiO_2, 250-nm TiO_2, 125, 500 µg instilled/rat	Particles instilled in male rats 24 h before they were killed and cells collected; cells cultured 18 h with 2-µm latex beads (5:1, bead:macrophage) to assess phagocytic activity	Phagocytic activity was significantly decreased relative to control for macrophages from rats instilled with all particle types/sizes at the 500-µg dose, but was unaffected at the 125-µg dose. At the 500-µg dose, phagocytosis tended to decrease progressively from fine TiO_2 to ultrafine TiO_2. Chemotactic activity of macrophages was significantly increased by ultrafine particles at the 500-µg dose, but was similar to saline control for fine particles and the low dose.	Renwick *et al*. (2004)
Skin from domestic pigs (5 months)	Titanium formulations (T-Lite), 10% TiO_2, needle-line particles of 30–60 nm×10 nm coated with methicone or methicone and silica; 400 µg/cm^2 or 240 µg/cm^2	Test formulations applied for 24 h to 1 cm^2 exposed skin (500 µm thick)	No dermal penetration of TiO_2 wasobserved for the tested suncreen formulations. Applied TiO_2 particles were mostly aggregates up to 200 nm and occasionally up to 1 µm. Virtually all the applied TiO_2 was recovered from skin surface by washing with sponge dipped in soap solution.	Gamer *et al*. (2006)

TITANIUM DIOXIDE

reported that Long-Evans rats (358 g) relative to smaller Fischer 344 rats (231 g) received a lower normalized total lung dose following a 7-hour exposure to titanium dioxide (0.43 versus 0.52 µg/g bw and 105 versus 114 µg/g lung, respectively).

Bellmann *et al.* (1991) found about 40% greater lung burdens of inhaled titanium dioxide in male Fischer 344 rats compared with similarly exposed female rats. When the mass of titanium dioxide was normalized to lung weight, however, lung burdens were similar between the males and females.

The method of delivery (instillation *versus* inhalation) affects the dose rate of particles delivered to the lungs as well as the distribution of these particles within the lungs and may also potentially affect observed pulmonary responses. The lobe-to-lobe distribution of inhaled titanium dioxide is associated with lobe weight (Ferin & Morehouse, 1980; Osier & Oberdörster, 1997). Osier and Oberdörster (1997) suggested that the increased response following instillation may be due to focal areas of high particle burden, differences in dose rate or clearance kinetics. Driscoll *et al.* (1991) also reported that, for similar lung burdens of titanium dioxide, instillation induced transient increases in levels of lavage protein and polymorphonuclear neutrophils that were not observed following inhalation exposures. Following a 12-week exposure to titanium dioxide, Oberdörster *et al.* (1994, 1997) measured the clearance kinetics of both fine and ultrafine titanium dioxide as well as the clearance of subsequently administered radiolabelled particles (3.3 µm). The method of delivery of this radiolabelled particle, i.e. by inhalation or instillation, did not appear to affect the measured pulmonary clearance rates.

At 25 days after inhalation exposure to a 1.0-µm MMAD titanium-dioxide aerosol, Ferin and Morehouse (1980) reported 70% particle retention in Fischer 344 rats while Long-Evans rats retained only 55%. However, Driscoll *et al.* (1991) only observed 39% retention in Fischer 344 rats 28 days after a 5-day exposure to a 1.0-µm MMAD titanium dioxide aerosol. Pulmonary clearance in rats is also affected by age, with typical retention half-times of 45 days at 5 months versus 74 days at 23 months (Muhle *et al.*, 1990).

The exposure history of animals also affects particle clearance. Exposure to the gaseous pollutants, nitrogen oxide and sulfur dioxide, stimulated particle clearance of titanium dioxide at low levels of exposure but suppressed clearance at higher levels of exposure (Ferin & Leach, 1975). The clearance might be due to macrophages and macrophage recruitment following initial exposure to gaseous pollutants would explain the stimulated clearance. Indeed, the chemotactic activity of macrophages is significantly increased following acute exposures to titanium dioxide (Renwick *et al.*, 2004). However, chronic exposures to high concentrations of titanium dioxide aerosols impaired alveolar clearance to varying degrees in rats and mice (Bermudez *et al.*, 2002, 2004) and possibly in hamsters (Creutzenberg *et al.*, 1998). Co-exposure of rats to cytotoxic aerosols impaired macrophage clearance of titanium dioxide and increased titanium dioxide translocation to the lymph system (Greenspan *et al.*, 1988).

Although differences have been observed between studies, common findings related to the behaviour of titanium dioxide particles in the respiratory tract have been reported. Following subchronic exposures to high concentrations, pulmonary clearance rates of fine

TITANIUM DIOXIDE 253

titanium-dioxide particles were decreased in both rats and mice and those of ultrafine titanium-dioxide particles were decreased to a greater extent. The evidence in hamsters is contradictory; two studies (Bermudez *et al*., 2002, 2004) showed no effect of subchronic exposure to titanium dioxide on clearance and one found impaired clearance (Creutzenberg *et al*., 1998). Rats, mice and hamsters all experienced acute inflammatory responses after exposure to fine and ultrafine titanium-dioxide particles, although the response was greater with ultrafine particles on a mass basis (Bermudez *et al*., 2002, 2004). Following exposures to titanium dioxide, rats and mice (but not hamsters) also demonstrated increased epithelial permeability which can affect the transport of titanium dioxide and other materials from the lumenal surfaces into the tissues and even the circulation.

Both in-vitro and in-vivo studies have demonstrated the rapid (~1 hour) translocation of free ultrafine-titanium dioxide particles across pulmonary cell membranes (Ferin *et al*., 1992; Churg *et al*., 1998; Geiser *et al*., 2005). Agglomerates of titanium dioxide particles may disassociate once deposited in the lungs; thus, inhaled agglomerate size is the determinant of the amount and site of deposition, but subsequent clearance is influenced by the properties of the agglomerates and the primary particles (Takenaka *et al*., 1986; Ferin *et al*., 1992; Bermudez *et al*., 2002). Following dissociation, ultrafine titanium dioxide particles are cleared more slowly and cause a greater inflammatory response (influx of polymorphonuclear neutrophils) than fine titanium dioxide particles (Ferin *et al*., 1992; Oberdörster *et al*., 1994, 2000; Bermudez *et al*., 2002, 2004). An increase in the transport by macrophages of titanium dioxide to lymph nodes has been reported following inhalation of a cytotoxin (Greenspan *et al*., 1988). However, Geiser *et al*. (2005) reported that ~80% of 22-nm titanium dioxide particles remained on the lumenal alveolar surface of rats 24 hours after inhalation. Both ultrafine and fine (0.078 and 0.2 μm in diameter) particles cross cellular membranes by non-endocytic (i.e. those that involve vesicle formation) mechanisms such as adhesive interactions and diffusion, whereas the phagocytosis of larger 1-μm particles is ligand receptor-mediated (Geiser *et al*., 2005). The differences in inflammatory effects and possibly lymph node burdens between fine and ultrafine titanium dioxide appear to be related to lung burden in terms of particle surface area and not particle mass or number (Oberdörster *et al*., 1992a; Oberdörster 1996; Oberdörster *et al*., 2000; Tran *et al*., 2000). The surface properties of titanium dioxide (e.g. roughness) may affect protein binding, and smoother titanium dioxide surfaces are more hydrophobic (Sousa *et al*., 2004).

The apparent dysfunction in pulmonary clearance as measured by lung burden of titanium dioxide following long-term exposure might not be representative for clearance of subsequently inhaled fine particles (ILSI Risk Science Institute Workshop Participants, 2000). When titanium-dioxide particles are sequestered, they may not necessarily influence nor would their clearance kinetics be reflective of macrophage-mediated removal of subsequently inhaled materials. For example, following a subchronic 12-week exposure, lung burdens of both silica and ultrafine titanium dioxide suggested impaired macrophage clearance (Oberdörster *et al*., 1994). The prolonged lung burdens were

presumed to be due to the cytotoxicity of silica dioxide and sequestration of ultrafine titanium dioxide in the interstitium. However, exposure to radiolabelled polystyrene (3.3 µm) particles also revealed a delay in clearance in animals exposed to both silica and ultrafine titanium dioxide. These large polystyrene particles were probably not sequestered even in the presence of increased epithelial permeability, and thus demonstrated impaired alveolar macrophage-mediated clearance.

4.2.2   *Toxic effects*

(a)   In vivo

As reported previously (IARC, 1989), administration of high doses of titanium dioxide to experimental animals by intraperitoneal or intrapleural injection or by intratracheal instillation into the lung resulted in varying degrees of inflammation with minimal associated pathology (lung damage or fibrosis). Some studies demonstrated the fibrotic potential of titanium dioxide in rats (Muhle *et al*., 1991) in contrast to a wide range of studies that failed to demonstrate any fibrotic potential of fine titanium dioxide in rats or rabbits (IARC, 1989; Ferin & Oberdörster, 1985). However, one study showed that intratracheal instillation of 3 mg titanium dioxide to hamsters once a week for 15 weeks resulted in slight pulmonary inflammation and, subsequently, pathological evidence of interstitial fibrosis (Stenbäck *et al*., 1976). Normal clearance pathways from the lung were impaired in rats that had been exposed to 250 mg/m^3 rutile for six hours per day on five days per week for two years, and massive accumulation of dust-laden macrophages was observed. In addition, free particles and cellular debris were found in the alveoli, and alveolar proteinosis and cholesterol granulomas developed. Lung weights were increased and white patches of accumulated material were seen in the lungs at necropsy (Lee *et al*., 1985a,b, 1986). The collective results from these studies are consistent with a breakdown of normal clearance functions and altered lung structure due to the massive amount of titanium dioxide retained. The lowest exposure concentration of 10 mg/m^3 showed minimal effects whereas the 50-mg/m^3 dose also showed evidence of overload. Most of the pathology and related changes were considered by the authors to be overload-dependent.

Several studies have expanded the understanding of the toxicity of titanium dioxide, especially under conditions of lower exposure. Moreover, studies that used ultrafine or nanosize titanium dioxide showed enhanced toxicity relative to the fine particles used in earlier studies (IARC, 1989).

Baggs *et al*. (1997) compared the inhalation toxicity of fine (250 nm) versus ultrafine (20 nm) titanium dioxide (~23 mg/m^3 for six hours per day on five days per week for three months) in male Fischer 344 rats. After six months in clean air following exposure, fine titanium dioxide induced a minor degree of fibrous changes at three months, as shown by trichrome collagen staining, which was less than that in the ultrafine-treated group. The fibrous deposits (indicated by staining) decreased after six months in clean air and then became not significantly greater than those in controls at 12 months. Ultrafine

TITANIUM DIOXIDE   255

particles were more fibroproliferative in rats than fine titanium dioxide, but the fibrotic lesions (generally thought to be permanent) appeared to be reversible. Earlier work by this group (Ferin & Oberdörster, 1992) showed that inhalation of fine (250 nm) or ultrafine (20 nm) titanium dioxide (~23 mg/m^3 for 6 hours per day on 5 days per week) for 12 weeks induced differential tissue uptake of the particles (most notably at 12 weeks of exposure) and that ultrafine titanium dioxide induced much more and increasing inflammation throughout the 12-week period of exposure. It was concluded that the ultrafine particles had probably passed into the lung epithelium after having escaped phagocytosis. Intratracheal instillation with 500 μg of each type of particle yielded largely analogous findings 1 and 29 days after treatment but inflammation returned to normal at 59 days in both treatment groups.

In related studies that used the same exposures, Oberdörster *et al*. (1992a,b) provided further evidence for heightened inflammation and associated pro-inflammatory mediators in the lungs of rats exposed to ultrafine titanium dioxide as well as for reduced clearance detected by a radiotracer. The impact of the particles on inflammation correlated better with surface area than with dose mass. Osier and Oberdörster (1997) also investigated fine (250 nm) and ultrafine (20 nm) titanium dioxide in a comparative study of intratracheal instillation versus inhalation that allowed an approximation of similar acute (single exposure) lung burdens (500 and 750 μg, respectively). Acute effects (e.g. inflammation) were quantitatively similar until 7 days after exposure and the differential potency was consistent with that previously noted for ultrafine and fine particles. Instillation elicited a greater intensity of response possibly due to differences in dose rate and a less dispersed distribution of particles in the distal lung. Similar results were reported by Renwick *et al*. (2004) but the differences between the size modes that were apparent in male Wistar rats instilled with 500 μg were not evident in those administered 125 μg.

Inhalation studies with fine titanium dioxide have generally been consistent with earlier findings that suggested that its toxicity is similar to that of other poorly soluble particles (ILSI Risk Science Institute Workshop Participants, 2000). Male HAN rats exposed for 3–30 days (on 5 days per week) to 50 mg/m^3 fine titanium dioxide and followed up to 75 days showed little or no evidence of toxicity (Brown *et al*., 1992). Tests for macrophage chemotaxis with the Boyden chamber at any time after exposure showed no stimulatory effect of titanium dioxide, which was consistent with the general lack of inflammation. A similar 5-day exposure (for 6 hours per day) to titanium dioxide (1 μm) was assessed for profibrotic inflammatory end-points 7–63 days after exposure (Driscoll *et al*., 1991). Lung burden was 1.8 mg at 5 days and retention was 38.6% 28 days after exposure. Bronchoalveolar lavage indices showed no evidence (cellular, enzyme or cytokine) of damage or inflammation, nor was there evidence of macrophage activation that might lead to fibrosis under the conditions of this study.

Inhalation of 5, 50 and 250 mg/m^3 pigment-grade (fine) titanium dioxide (~1.7 μm) for 6 hours per day on 5 days per week for 4 weeks by male Crl:CDBR rats was evaluated for various inflammation-related end-points at 1 week and 1, 3 and 6 months after

exposure (Warheit *et al*., 1997). Effects consistent with prolonged (but slowly decreasing) inflammation and macrophage impairment were generally limited to the 250-mg/m^3 exposure group (12 mg retained dose). The lower-exposure groups recovered in an inverse dose-dependent manner. Pathology reflected the retained titanium dioxide in aggregated particle-laden macrophages and foamy cells, with no evidence of significant fibrosis.

Instillation of titanium dioxide (200 μg) [size of the dust particles not specified] into female C3H/He mice did not alter the clonal activity of macrophages harvested 40 days after exposure, which would be consistent with the unimpaired health of macrophages and the lack of evidence of profibrotic activity (Oghiso *et al*., 1992). A much broader array of pulmonary and systemic immunological end-points were evaluated in Fischer 344 rats exposed for 8 consecutive days (~40 mg/m^3; 2.2 μm; σ_g=1.4; 5 hours per day) (Huang *et al*., 2001). Assays up to 5 months after exposure showed minimal if any impact on associated immune function and cell mediators.

Several studies of subchronic to chronic duration have compared particle sizes and species responses to relatively low levels of titanium dioxide. Henderson *et al.* (1995) exposed female Fischer 344 rats to 0, 0.1, 1.0 and 10 mg/m^3 fine commercial-grade titanium dioxide by inhalation for 4 weeks (6 hours per day on 5 days per week). Lung burdens ranged from 4.4 to 440 μg after 1 week. Other groups of rats received instillations of 50, 200 and 750 μg to parallel these groups; higher doses were used due to the lack of apparent effects of the titanium dioxide. Measurement of cells, enzyme and cytokine markers and pathological lesions showed no effect of titanium throughout the study (1, 8 and 24 weeks after exposure) for either inhalation or instillation exposures.

Bermudez *et al*. (2002, 2004) exposed female rats, mice and hamsters by inhalation to fine (rutile; 250-nm primary particles) and ultrafine (21-nm primary particles) titanium dioxide (see Table 4.1 for details of exposure). In the study of fine titanium dioxide (Bermudez *et al*. 2002), particles accumulated in all species at 10 mg/m^3 and all species cleared the particles substantially during the period after exposure (rats>mice>hamsters), although hamsters cleared particles more completely than mice and mice more completely than rats by 1 year after exposure. At 50 and 250 mg/m^3, mice and rats accumulated more particles than hamsters and both were in overload within a minimal period after exposure in contrast to the nearly complete clearance in hamsters. Bronchoalveolar lavage indices of lung injury and inflammation at the high concentrations showed high neutrophil responses in all species and reversal in rats and mice was retarded (rat > mouse) in comparison with hamsters. Significant inflammation (but to a much much lesser extent than that with the high-level exposures) occurred in rats at 10 mg/m^3. Inflammation markers generally followed this pattern. Rats exposed to concentrations of 50 and 250 mg/m^3 developed a dose-dependent accumulation of dust in the cells, hyperplasia and alveolar lipoproteinosis. Minute collagenized fibrosis occurred in the alveolar walls that enclosed large dust–cell aggregates. The nature of the lesions in rats appeared to be actively fibroproliferative compared with those in mice and hamsters.

TITANIUM DIOXIDE 257

Indices of epithelial cell proliferation in the end airways and alveoli were seen primarily in rats and were persistent.

In the study of ultrafine titanium dioxide, Bermudez *et al*. (2004) reported that mice and rats had similar normalized lung burdens but that mice appeared to clear the particles faster than rats, except at 10 mg/m^3 when they were almost identical and appeared to have arrested clearance. In contrast, hamsters exhibited rapid clearance regardless of the exposure level. Bronchoalveolar lavage indices of lung injury and inflammation showed a greater neutrophil response in rats across the ranges of concentrations and mice showed an early high macrophagic response that decreased to below that of rats over time. Pathology (septal thickening and fibrosis) generally followed these patterns (hamsters had virtually none) and the nature of the lesions in rats appeared to be actively fibroproliferative compared with those of mice and hamsters. Indices of epithelial cell proliferation in the end airways were consistent with these observations; the reversal after exposure was most rapid in hamsters.

The impact of surface treatment on the acute lung toxicity of titanium dioxide particles was assessed in a short-term pulmonary assay with Crl:CD(SD)/GS BR rats. The particles used were R-100 titanium dioxide (1 wt% alumina; average size, 300 nm; average surface area, 6 m^2/g) and Pigment A titanium dioxide (1 wt% alumina, 3 wt% amorphous silica encapsulating the particle; average size, 290 nm; average surface area, 7.9 m^2/g), both of which were in the rutile form. Rats received a single dose of 1 or 5 mg/kg bw of the particles dispersed in phosphate buffered saline. Bronchoalveolar lavages were conducted 24 hours, 1 week, 1 month and 3 months after instillation. The inflammatory response to titanium dioxide particles was transient; this may have been the result of the instillation process itself as it was also seen in the vehicle-control group. Similar responses were observed with the lavage fluid parameters (lactate dehydrogenase, microprotein and alkaline phosphatase) and similar results were seen in the rate of lung parenchymal cell proliferation. Histopathological analyses of lung tissues showed no significant adverse effects of titanium dioxide (both types) (Warheit *et al*., 2005).

A 2-year chronic inhalation study with commercial-grade titanium dioxide (~1.6 μm; 0, 10, 50 and 250 mg/m^3 for 6 hours per day on 5 days per week) demonstrated the transmigration of particles to systemic tissues, notably the liver and spleen (Lee *et al*., 1985a,b). The authors surmised from the minimal presence of particles not associated with immune or phagocytic cells that the dose-dependent systemic evidence of particles was indicative of transmigration through the lymphatic system into the blood. There was evidence of mild focal fibrosis with few apparent interstitial particles.

Muhle *et al*. (1990, 1991) reported a series of studies that involved exposure of rats and hamsters to rutile and anatase titanium dioxide (5–30 mg/m^3) and described overload and mild inflammation in both species, although the condition appeared to be more severe (based on pathology) in rats. The anatase form was somewhat more potent in rats than the rutile form, which may reflect the 10-fold smaller size of the anatase (0.02–0.04 μm versus 0.2–0.7 μm). Pathological evidence of fibrogenesis was reported in rats.

258   IARC MONOGRAPHS VOLUME 93

> *(b)   In vitro*

Iyer *et al*. (1996) found that primary human macrophages cultured for up to 24 hours with 60 μg/mL commercial-grade titanium dioxide (0.45 μm) did not show apoptosis or any other evidence of DNA damage that might initiate profibrotic inflammation.

Pro-inflammatory pathways that involve IκBα degradation were assessed by examining its linkage to interleukin (IL)-8 expression (Schins *et al*., 2000) in A549 epithelial cell cultures treated with commercial fine titanium dioxide (40 μg/cm^2). Degradation of IκBα correlated with a brief induction of IL-8 (a pro-inflammatory cytokine) that rapidly decreased; this led the authors to conclude that titanium dioxide has transient but probably minimal inflammatory potential.

In a rat nasal epithelial model that predicts upper respiratory tract toxicity *in vivo* and *in vitro* (Kilgour *et al*., 2000), nasal turbinates from mice were incubated with titanium dioxide, and adenosine triphosphate was evaluated in the nasal olfactory epithelium or respiratory epithelium. Titanium dioxide caused little or no loss of adenosine triphosphate in either.

The in-vitro toxicity of ultrafine titanium dioxide particles (40 nm) was assessed by cell morphology, mitochondrial function, membrane leakage of lactate dehydrogenase and reduced glutathione levels as well as the release of reactive oxygen species in mitochondrial membrane potential (Hussain *et al*., 2005). Titanium dioxide was used as a negative control based on published data that ultrafine particles of titanium dioxide show no toxicity to these cells. Titanium dioxide appeared to have the lowest level of toxicity to cells for any of these parameters.

Donaldson and Brown (1988) compared the rutile form of titanium dioxide (medium volume diameter, 2.4 μm) with crocidolite asbestos and quartz. Rat alveolar macrophages released ^{51}Cr (indicative of cell damage) in significantly lower quantities after exposure to titanium dioxide than after exposure to either crocidolite asbestos or quartz.

Yamamoto *et al*. (2004) tested the cytotoxicity of ceramic particles of different sizes and shapes and found that dendritic particles of titanium dioxide had significantly greater toxicity than those that were spherical or spindle shaped.

Human skin fibroblasts preincubated for 18 hours with 10 μg/cm^2 titanium dioxide (anatase, 450 nm) and then irradiated with UVA showed dose-dependent photocytotoxicity, which suggested that nucleic acids are a potential target for photo-oxidative damage that has been sensitized with titanium dioxide (Wamer *et al*., 1997).

Stringer and Kobzik (1998) evaluated the effect of titanium dioxide in increasing IL-8 production in primed A549 human lung epithelial cells and found that it caused significantly less tumour necrosis factor -α and IL-8 release than residual oil fly ash or pathogenic α-quartz dust. Using a mouse macrophage cell line, Thibodeau *et al*. (2003) found that exposure to α-quartz silica elicited activation of caspase 3 and caspase 9, whereas exposure to titanium dioxide did not.

Exposure of mouse peritoneal macrophages *in vitro* to 100 μg/mL titanium dioxide in the culture medium was found to inhibit the phagocytic activity of cells compared with controls (Nuuja & Arstila, 1982). The phagocytosis of alveolar macrophages was

impaired following exposure to ultrafine particles including titanium dioxide (Renwick *et al*., 2001). Oberdörster *et al*. (1992a) found that alveolar macrophages exposed to ultrafine titanium dioxide (12 and 20 nm diameter) have a greater potential to induce cytokines than those exposed to larger-sized particles.

Li (1986) and Li and Myers (1988) found that titanium dioxide caused significantly less damage than chrysotile or calcite fibres in airway epithelial cells using an in-vitro lung epithelial cell system for evaluating the potential toxicity of inhalable material. Titanium dioxide was far less toxic than calcium sulfate, chrysotile crocidolite and phosphate fibres.

4.2.3   *Genetic and related effects*

Investigations on the genetic and related effects of titanium dioxide have been performed using isolated DNA and cell culture-based test systems, as well as animals. In several of these studies titanium dioxide was used as a negative control. Other studies have evaluated the toxic properties of titanium dioxide in relation to its size (e.g. fine versus ultrafine) and/or chemistry (e.g. anatase versus rutile). Several studies have also addressed the photosensitization effects of titanium dioxide. In view of the contrasting photocatalytic and biological activities of titanium dioxide in relation to size and chemical composition (Oberdörster *et al*., 2005), specifications of each sample tested are provided whenever available.

(a)   Isolated DNA

Unwinding and breakage of plasmid DNA *in vitro* has been used to investigate the generation of reactive oxygen species by various mineral dusts including titanium dioxide (Donaldson *et al*., 1996). [The Working Group noted the limited relevance of this assay for assessing particle-induced genetic damage]. A comparison of fine (500 nm) *versus* ultrafine (20 nm) titanium dioxide using ΦX174 RF plasmid DNA showed markedly stronger strand breakage for the ultrafine sample. DNA damage by the ultrafine titanium dioxide was prevented by the presence of mannitol, which suggests that the damaging effects were due to hydroxyl radicals (Donaldson *et al*., 1996). In contrast, in a more recent study, ultrafine titanium dioxide (20 nm; 49.8 m^2/g) failed to damage ΦX174 RF DNA unlike various other particles of similar size (Dick *et al*., 2003). [Different incubation times as well as different relative amounts of plasmid DNA and titanium dioxide were used in the two studies.]

The effects of UV light-irradiated titanium dioxide on isolated DNA have been investigated. Upon co-exposure with simulated sunlight (300–400 nm), both the anatase and rutile forms [particle size not specified] of titanium dioxide induced damage in pBluescript II SK$^+$ plasmid DNA; anatase showed stronger effects than rutile (Dunford *et al*., 1997). Photo-irradiated (365 nm; UVA) anatase and rutile (size range, 50–300 nm) also caused the formation of 8-hydroxy-2′-deoxyguanosine in calf thymus DNA in the presence of copper chloride (Hirakawa *et al*., 2004). Again, anatase showed stronger effects than rutile. In the absence of irradiation, no DNA damage was found. Following

260   IARC MONOGRAPHS VOLUME 93

irradiation, both samples also showed enhanced formamidopyrimidine glycosylase-mediated cleavage of DNA fragments that contained human tumour-suppressor genes *P53* and *P16* and the c-Ha-*RAS*-1 oncogene (Hirakawa *et al.*, 2004). Oxidative damage in calf thymus DNA was also reported after combined treatment with UVA (320–400 nm) and titanium dioxide (average size, 450 nm) (Wamer *et al.*, 1997).

(b)   Cellular effects (for details and references, see Table 4.4)

Anatase titanium dioxide (21 nm) was not mutagenic to *Salmonella typhimurium* TA100, TA98 or TA102. Titanium dioxide [unspecified] did not induce somatic mutation or recombination in *Drosophila melanogaster.*

Anatase (255 nm) but not 21-nm anatase or rutile (255 or 420 nm) titanium dioxide caused DNA strand breaks in mouse lymphoma L5178Y cells. Induction of oxidative DNA damage (8-hydroxy-2′-deoxyguanosine formation) was seen in rat lung epithelial cells treated with 180-nm anatase titanium dioxide. Anatase titanium dioxide did not enhance unscheduled DNA synthesis in rat pleural mesothelial cells or induce mutation in mouse lymphoma L5178Y/tk$^{+/-}$ or RLE-6TN rat lung epithelial cells.

Titanium dioxide caused a dose-dependent increase in sister chromatid exchange in Chinese hamster CHO-K1 cells at non-toxic concentrations but not in rat pleural mesothelial or Chinese hamster ovary CHO cells. No micronucleus formation was found in Chinese hamster ovary CHO cells incubated with titanium dioxide either in the presence or absence of metabolic activation. In contrast, titanium dioxide did induce micronuclei in Chinese hamster CHO-K1 cells. Titanium dioxide samples of different size or chemistry did not cause micronucleus formation in RLE rat liver epithelial cells, but a sample of ultrafine (≤20 nm) titanium dioxide did induce micronuclei in Syrian hamster fibroblasts, while >200-nm titanium dioxide was inactive. The ultrafine sample also elicited apoptosis in these cells. Titanium dioxide did not include chromosomal aberrations in Chinese hamster CHU/IU cells (21-nm anatase), Chinese hamster CHO cells or rat pleural mesothelial cells (anatase [size unspecified]). Titanium dioxide did not cause cell transformation of Syrian hamster embryo or mouse BALB/3T3/31–1-1 cells.

Enhanced oxidative DNA damage was observed in BEAS-2B human bronchial epithelial cells with 10-nm and 20-nm anatase and 200-nm rutile. A 1:1 mixture of 200-nm anatase and 200-nm rutile caused stronger oxidative DNA damage than either of these alone. No oxidative DNA damage was observed in CRL human skin fibroblasts [unspecified titanium dioxide]. DNA strand breakage assays (alkaline unwinding) in WI-26 human embryonal lung cells showed negligible effects of titanium dioxide [unspecified]. The compound did not induce mitochondrial dysfunction (i.e. membrane potential change) in A549 human lung epithelial cells. In BEAS-2B human bronchial epithelial cells, micronucleus formation was induced with 10-nm and 200-nm anatase titanium dioxide (not with >200-nm anatase or 200-nm rutile). Increased multinucleation was found in Met-5A human mesothelial cells treated with titanium dioxide [unspecified], but no such effect was observed in primary human mesothelial cells.

Table 4.4. Genetic and related effects of titanium dioxide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA102, TA98, reverse mutation	–	NT	40 000 µg/mL (21-nm anatase)	Nakagawa *et al.* (1997)
Drosophila melanogaster, wing mosaic assay	–		300 mM[c]	Tripathy *et al.* (1990)
DNA strand breaks (comet asssay), mouse lymphoma L5178Y/tk^{+/–} cells *in vitro*	+	NT	800 µg/mL (255-nm anatase)	Nakagawa *et al.* (1997)
DNA strand breaks (comet assay), mouse lymphoma L5178Y/tk^{+/–} cells *in vitro*	–	NT	3200 µg/mL (255-nm rutile; 420-nm rutile); 800 µg/mL (21-nm anatase)	Nakagawa *et al.* (1997)
Oxidative DNA damage, RLE rat lung epithelial cells *in vitro*	+	NT	1700 µg/mL	van Maanen *et al.* (1999)
Unscheduled DNA synthesis, rat pleural mesothelial cells *in vitro*	–	NT	50 µg/mL (anatase) (10 µg/cm^2)[d]	Endo-Capron *et al.* (1993)
Gene mutation, L5178Y/tk^{+/–} mouse lymphoma cells *in vitro*	–	NT	2000 µg/mL (21-nm anatase)	Nakagawa *et al.* (1997)
Gene mutation, *Hprt* locus, RLE-6TN rat lung epithelial cells *in vitro*	–	NT	100 µg/cm^2 (180-nm anatase)	Driscoll *et al.* (1997)
Sister chromatid exchange, Chinese hamster CHO-K1 cells *in vitro*	+	NT	1 µM[c]	Lu *et al.* (1998)
Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	25 µg/mL	Ivett *et al.* (1989)
Sister chromatid exchange, RLE rat pleural mesothelial cells *in vitro*	–	NT	37.5 µg/mL (5 µg/cm^2)	Endo-Capron *et al.* (1993)
Micronucleus formation, Chinese hamster CHO-K1 cells *in vitro*	+	NT	2 µM[c]	Lu *et al.* (1998)

Table 4.4 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, Chinese hamster CHO cells *in vitro*	–	–	10 µg/mL	Miller *et al.* (1995)
Micronucleus formation, RLE rat liver epithelial cells *in vitro*	–	NT	20 µg/cm^2 (20-nm anatase; 170-nm rutile)	Linnainmaa *et al.* (1997)
Micronucleus formation, Syrian hamster embryo cells *in vitro*	+	NT	1 µg/cm^2 (ultrafine ≤20 nm)	Rahman *et al.* (2002)
Micronucleus formation, Syrian hamster embryo cells *in vitro*	–	NT	10 µg/cm^2 (fine[e] >200 nm)	Rahman *et al.* (2002)
Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	25 µg/mL	Ivett *et al.* (1989)
Chromosomal aberrations, Chinese hamster CHU/IU cells *in vitro*	–	NT	800 µg/mL (21-nm anatase)	Nakagawa *et al.* (1997)
Chromosomal aberrations, rat pleural mesothelial cells *in vitro*	–	NT	10 µg/cm^2 (anatase)	Yegles *et al.* (1993)
Cell transformation, BALB/3T3/A31-1-1 mouse cells	–	NT	100 µg/cm^2 (anatase; rutile)	Saffiotti & Ahmed (1995–1996)
Cell transformation, Syrian hamster embryo cells	–	NT	75 µg/mL	LeBoeuf *et al.* (1996)
DNA strand breaks (alkaline unwinding), WI-26 human embryonal lung cells *in vitro*	–	NT	500 µg/mL	Kamp *et al.* (1995)
Oxidative DNA damage, CRL1634 human skin fibroblasts *in vitro*	–	NT	71.4 µg/mL (10 µg/cm^2)	Wamer *et al.* (1997)
Oxidative DNA damage (FPg-comet assay), human BEAS-2B bronchial epithelial cells *in vitro*	+	NT	10 µg/mL (1.77 µg/cm^2) 10-nm anatase, 20-nm anatase, 200-nm rutile	Gurr *et al.* (2005)

Table 4.4 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, Met-5A human mesothelial cell line *in vitro*	+	NT	2 μg/cm^2 [unspecified]	Pelin *et al.* (1995)
Micronucleus formation, primary human mesothelial cells *in vitro*	–	NT	5 μg/cm^2 [unspecified]	Pelin *et al.* (1995)
Micronucleus formation, human BEAS-2B bronchial epithelial cells *in vitro*	–	NT	10 μg/mL (1.77 μg/cm^2) 200-nm rutile, >200-nm anatase	Gurr *et al.* (2005)
Micronucleus formation, human BEAS-2B bronchial epithelial cells *in vitro*	+	NT	10 μg/mL (1.77 μg/cm^2) 10-nm anatase, 200-nm anatase,	Gurr *et al.* (2005)
Oxidative DNA damage, rat lung *in vivo*	–		2×50 mg/kg it (180 nm anatase)	Driscoll *et al.* (1997)
Gene mutation, *Hprt* locus, rat alveolar epithelial cells *in vivo*	+		100 mg/kg it (180 nm anatase)	Driscoll *et al.* (1997)
Micronucleus formation, mouse bone-marrow cells, peripheral blood lymphocytes *in vivo*	+		1000 mg/kg, ip×3	Shelby *et al.* (1993)

[a] +, positive; –, negative; NT, not tested;
[b] HID, higher inhibitory dose; LED, lower efficient dose, in-vitro tests, μg/mL; in-vivo tests, mg/kg bw; ip, intraperitoneal; it, intratracheal
[c] Dose expressed in molarity
[d] One of three experiments was positive.
[e] Dose for fine sample not specified in detail ['similar' concentrations were used for fine and ultrafine]

(c)   Cellular effects in combination with UV irradiation

In relation to its application in sunscreens or its photocatalytic activity, several studies have addressed the effects photo-irradiated titanium dioxide. Micronucleus formation was not enhanced in rat liver epithelial cells after treatment with 170-nm anatase, 20-nm anatase or 20-nm aluminium hydroxide/stearic acid-coated rutile in combination with irradiation with UVA (at 365 nm wavelength) (Linnainmaa *et al*., 1997). In contrast, irradiated (300–400 nm wavelength) MRC-5-fibroblasts showed increased DNA strand breakage in the presence of anatase or rutile [sizes not specified] compared with cells irradiated in the absence of titanium dioxide (Dunford *et al*. 1997). In human skin fibroblasts (CRL1634, ATCC), enhanced oxidation of RNA was observed following combined titanium dioxide (particle size, 450 nm) plus UVA (320–400 nm). Treatment with titanium dioxide plus UVA did not cause increased oxidative damage to DNA (Wamer *et al*., 1997). Four titanium dioxide samples, i.e. a 21-nm anatase, a 255-nm anatase, a 255-nm rutile and a 420-nm rutile, were tested in an assay that measured DNA strand breakage in L5178Y/tk$^{+/-}$ mouse lymphoma cells. In the presence of UV light, all samples induced enhanced DNA strand breakage as determined by the alkaline comet assay at concentrations that also caused cell death (Nakagawa *et al*., 1997). In the same study, the 21-nm anatase sample induced chromosomal aberrations in the Chinese hamster CHL/IU cell line in the presence but not in the absence of UV/visible light. Besides polyploidy, the principal structural aberrations that occurred after treatment with 21-nm titanium dioxide plus UV light were chromatid breaks and chromatid exchanges, which occurred at cytotoxic concentrations (Nakagawa *et al*., 1997). The same sample was not mutagenic in *S. typhimurium* strains TA100, TAS98 or TA102, or when tested in an L5178Y/tk$^{+/-}$ colony formation assay when irradiated with UV light (Nakagawa *et al*., 1997).

(d)   Studies in rodents (see also Table 4.4)

The induction of oxidative DNA damage in rat lungs was investigated after intratracheal instillation with two different samples of titanium dioxide, i.e. an untreated titanium dioxide (P-25, hydrophilic surface) and a trimethoxyoctylsilane-treated titanium dioxide (T-805, silanised/hydrophobic surface; particle size, ~20 nm). Transmission electron microscopy demonstrated a highly aggregated state of both titanium dioxide samples. Oxidative damage, as determined at 90 days in lung sections using 8-oxoguanine antibody, was not enhanced by untreated or silanised titanium dioxide (Rehn *et al*., 2003).

In-vivo mutagenesis of titanium dioxide (anatase; 180 nm median diameter; 8.8 m^2/g) was studied by *Hprt* analysis of epithelial cells isolated from the lungs of female SPF F344 Fischer rats 15 months after intratracheal instillation. Enhanced *Hprt* mutagenesis was observed with 100 mg/kg bw, a dose that also elicited persistent lung inflammation. The authors suggested that the in-vivo mutagenesis was driven by inflammation (Driscoll *et al*., 1997).

Intraperitoneal injection of titanium dioxide into mice resulted in enhanced micronucleus formation in bone-marrow cells and peripheral blood lymphocytes. No dose-dependent effect was observed over the range of 200–1000 mg/kg bw (Shelby *et al*., 1993).

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268   IARC MONOGRAPHS VOLUME 93

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TITANIUM DIOXIDE   271

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5. Summary of Data Reported

5.1   Exposure data

Titanium dioxide was first produced commercially in 1923, primarily for pigment production. Relatively small quantities of titanium dioxide are used for non-pigmentary purposes. In 2004, worldwide production of titanium dioxide was 4.4 million tonnes.

Titanium dioxide is obtained from a variety of ores that contain ilmenite, rutile, anatase and leucoxene, which are mined from deposits located throughout the world. Most titanium dioxide pigment is produced from titanium mineral concentrates by the chloride or sulfate process, either as the rutile or the anatase form. The primary particles are typically between 0.2 and 0.3 μm in diameter, although larger aggregates and agglomerates are formed. Ultrafine grades of titanium dioxide have a primary particle size of 10–50 nm and are used predominantly as ultraviolet blockers in sunscreens and plastics, and in catalysts. Most commercial titanium dioxide products are coated with inorganic (e.g. alumina, zirconia, silica) and organic (e.g. polyols, esters, siloxanes, silanes) compounds to control and improve surface properties.

Levels of occupational exposure to titanium dioxide during its manufacture have been reported from the USA and Europe between 1970 and 2000. The highest levels of exposure were observed during packing and milling, although high peak exposure also occurred in occupations such as site cleaning and maintenance. Average levels of exposure to respirable dust in these occupations up to 6 mg/m^3 (geometric mean) were reported, but have declined over time. No data were available that would allow the characterization or quantification of exposure to ultrafine primary particles. Workers in the titanium dioxide manufacturing industry may also be exposed to ore and other dusts, strong acids and asbestos.

Exposure to titanium dioxide in user industries is difficult to estimate and characterize due to the paucity of data. Exposure levels are assumed to be low in the user industries, with the possible exception of workers who handle large quantities of titanium dioxide. No significant exposure to titanium dioxide is thought to occur during the use of products in which titanium dioxide is bound to other materials, such as in paints.

5.2   Human carcinogenicity data

Three epidemiological cohort studies and one population-based case–control study from North America and western Europe were available for evaluation.

The largest of the cohort studies was among white male production workers in the titanium dioxide industry in six European countries. The study indicated a slightly increased risk for lung cancer compared with the general population. However, there was no evidence of an exposure–response relationship within the cohort. No increase in the

mortality rates for kidney cancer was found when the cohort was compared with the general population, but there was a suggestion of an exposure–response relationship in internal analyses. The other cohort studies, both of which were conducted in the USA, did not report an increased risk for lung cancer or cancer at any other site; no results for kidney cancer were reported, presumably because there were few cases.

One population-based case–control study conducted in Montréal did not indicate an increased risk for lung or kidney cancer.

In summary, the studies do not suggest an association between occupational exposure to titanium dioxide as it occurred in recent decades in western Europe and North America and risk for cancer.

All the studies had methodological limitations; misclassification of exposure could not be ruled out. None of the studies was designed to assess the impact of particle size (fine or ultrafine) or the potential effect of the coating compounds on the risk for lung cancer.

5.3   Animal carcinogenicity data

Pigmentary and ultrafine titanium dioxide were tested for carcinogenicity by oral administration in mice and rats, by inhalation exposure in rats and female mice, by intratracheal administration in hamsters and female rats and mice, by subcutaneous injection in rats and by intraperitoneal administration in male mice and female rats.

In one inhalation study, the incidence of benign and malignant lung tumours was increased in female rats. In another inhalation study, the incidence of benign lung tumours was increased in the high-dose groups of male and female rats. Cystic keratinizing lesions that were diagnosed as squamous-cell carcinomas but re-evaluated as non-neoplastic pulmonary keratinizing cysts were also observed in the high-dose groups of female rats. Two inhalation studies in rats and one in female mice gave negative results.

Intratracheally instilled female rats showed an increased incidence of both benign and malignant lung tumours following treatment with two types of titanium dioxide. Tumour incidence was not increased in intratracheally instilled hamsters and female mice.

Oral, subcutaneous and intraperitoneal administration did not produce a significant increase in the frequency of any type of tumour in mice or rats.

5.4   Mechanistic considerations and other relevant data

Humans can be exposed to titanium dioxide via inhalation, ingestion or dermal contact. In human lungs, the clearance kinetics of titanium dioxide is poorly characterized relative to that in experimental animals. (General particle characteristics and host factors that are considered to affect deposition and retention patterns of inhaled, poorly soluble particles such as titanium dioxide are summarized in the monograph on carbon black.) With regard to inhaled titanium dioxide, human data are mainly available from case reports that showed deposits of titanium dioxide in lung tissue as well as in lymph nodes.

A single clinical study of oral ingestion of fine titanium dioxide showed particle size-dependent absorption by the gastrointestinal tract and large interindividual variations in blood levels of titanium dioxide. Studies on the application of sunscreens containing ultrafine titanium dioxide to the healthy skin of human volunteers revealed that titanium dioxide particles only penetrate into the outermost layers of the stratum corneum, suggesting that healthy skin is an effective barrier to titanium dioxide. No studies on the penetration of titanium dioxide in compromised skin were available.

Respiratory effects that have been observed among groups of titanium dioxide-exposed workers include a decline in lung function, pleural disease with plaques and pleural thickening, and mild fibrotic changes. However, the workers in these studies were also exposed to asbestos and/or silica.

No data were available on the genotoxic effects in titanium dioxide-exposed humans.

Many data on deposition, retention and clearance of titanium dioxide in experimental animals are available for the inhalation route. Titanium dioxide inhalation studies showed differences—both for normalized pulmonary burden (deposited mass per dry lung, mass per body weight) and clearance kinetics—among rodent species including rats of different size, age and strain. Clearance of titanium dioxide is also affected by pre-exposure to gaseous pollutants or co-exposure to cytotoxic aerosols. Differences in dose rate or clearance kinetics and the appearance of focal areas of high particle burden have been implicated in the higher toxic and inflammatory lung responses to intratracheally instilled versus inhaled titanium dioxide particles. Experimental studies with titanium dioxide have demonstrated that rodents experience dose-dependent impairment of alveolar macrophage-mediated clearance. Ultrafine primary particles of titanium dioxide are cleared more slowly than their fine counterparts.

Titanium dioxide causes varying degrees of inflammation and associated pulmonary effects including lung epithelial cell injury, cholesterol granulomas and fibrosis. Rodents experience stronger pulmonary effects after exposure to ultrafine titanium dioxide particles compared with fine particles on a mass basis. These differences are related to lung burden in terms of particle surface area, and are considered to result from impaired phagocytosis and sequestration of ultrafine particles into the interstitium.

Fine titanium dioxide particles show minimal cytotoxicity and inflammatory/profibrotic mediator release from primary human alveolar macrophages *in vitro* compared with other particles. Ultrafine titanium dioxide particles inhibit phagocytosis of alveolar macrophages *in vitro* at mass dose concentrations at which this effect does not occur with fine titanium dioxide.

In-vitro studies with fine and ultrafine titanium dioxide and purified DNA show induction of DNA damage that is suggestive of the generation of reactive oxygen species by both particle types. This effect is stronger for ultrafine than for fine titanium dioxide, and is markedly enhanced by exposure to simulated sunlight/ultraviolet light.

In-vivo studies have shown enhanced micronucleus formation in bone marrow and peripheral blood lymphocytes of intraperitoneally instilled mice. Increased *Hprt* mutations were seen in lung epithelial cells isolated from titanium dioxide-instilled rats. In

TITANIUM DIOXIDE   275

another study, no enhanced oxidative DNA damage was observed in lung tissues of rats that were intratracheally instilled with titanium dioxide.

Most in-vitro genotoxicity studies with titanium dioxide gave negative results.

6. Evaluation and Rationale

6.1   Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of titanium dioxide.

6.2   Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of titanium dioxide.

6.3   Overall evaluation

Titanium dioxide is *possibly carcinogenic to humans (Group 2B)*.

6.4   Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as the evidence regarding potential mechanisms through which titanium dioxide might cause cancer in humans.

The Working Group found little evidence of an increased risk for cancer among humans based on epidemiological data, although relatively few studies were available. The single most informative study was a multicountry study of titanium dioxide production workers that found a slightly increased risk for lung cancer compared with the general population and a suggestive dose–response, but no overall excess risk for kidney cancer. The two other cohort studies reported no increased risks and evidence from the case–control study did not indicate an increased risk for either lung or kidney cancer. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether titanium dioxide causes cancer in humans.

In two studies of rats that inhaled titanium dioxide, one observed an excess incidence of lung tumours in both sexes and another in females only. Studies of rats exposed intratracheally found increases in the incidence of lung tumours. No increases were observed among mice and hamsters exposed intratracheally. Other studies that used different routes of administration did not observe excesses in tumour incidence. On the basis of the results of an increased incidence of lung tumours in rats, the Working Group

concluded that there was *sufficient evidence* that titanium dioxide is carcinogenic in experimental animals.

The Working Group considered the body of evidence regarding the pathways and mechanisms by which titanium dioxide or other poorly soluble particles may cause cancer. Following the same line of reasoning as that for the other particles reviewed in this volume, the Working Group considered that the available mechanistic evidence for titanium dioxide was not strong enough to warrant a classification other than Group 2B.

TALC NOT CONTAINING ASBESTIFORM FIBRES

1. Exposure Data

Introduction

Talc refers to both mineral talc and industrial mineral products that are marketed under the name talc and contain proportions of mineral talc that range from about 35% to almost 100%.

The mineralogy of airborne particles in talc mines is restricted by that of the deposit and associated rocks. Therefore, mines and mills provide an opportunity to characterize exposure to one specific source of talc mineralogically. In contrast, the mineralogy of talc in an industrial setting where talc products are used may be difficult to characterize, because many different sources of talc are available for almost every application. Industrial talcs are quite variable in their talc content and in the identity and proportion of other minerals that they contain. In addition, talc is part of a complex mixture of materials in user industries.

Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibres and have been identified as such. Talc may also form as true mineral fibres that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a 'habit'. Asbestiform talc fibres are very long and thin and occur in parallel bundles that are easily separated from each other by hand pressure.

Asbestos is a commercial term that describes six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite (IARC, 1977). Similarly to talc, these six minerals occur more commonly in a non-asbestiform habit, and may also be elongated without being asbestiform. Actinolite, anthophyllite and tremolite may occur in some talc deposits; when asbestiform, they constitute asbestos and, when not asbestiform, they are referred to as mineral fragments or cleavage fragments.

1.1   Chemical and physical data

1.1.1   *Nomenclature*

CAS Registry No.: 14807–96–6
Chem. Abstr. Name: Talc
Synonyms[1]: Soapstone; steatite; talcum
Trade names[1]: Trade names of industrial, cosmetic and pharmaceutical talc include Agalite, Asbestine, Australian microcrystalline, Beaver White 200, CP 10–40, CP 38–33, Crystalite CR 6002, Desertalc 57, Emtal 500, Emtal 549, Emtal 596, Emtal 599, Ex-IT, Fibrene C 400, Finntalc, French Chalk, FW-XO, HSDB 830, IT Extra, LMR 100, Microneeca K1, Micro White 5000A, Microtalco IT Extra, Mistron, Montana talc, MP 25–38, MP 40–27, MP 45–26, MST, MT 12–50, Mussolinite, NCI-CO6018, Nytal 200, Nytal 400, Pk-C, Pk-N, Plustalc, Polytal 4641, Polytal 4725, Snowgoose, Steawhite, Supreme, Supreme dense, Talcan PK-P, Talcron CP 44–31 and Westmin.

Rocks or mineral composites that contain talc mineral include agalite, potstone, soapstone and talcite. Soapstone generally contains at least 25% of minerals other than talc while talcite is sometimes used to describe rock that contains at least 75% talc (Harben & Kuzvart, 1996). Steatite originally referred to a rock that is relatively pure talc; today, it denotes a ceramic body with a high talc content that is used as an electrical insulator. The talc that is used in such applications is known as steatitic talc. French chalk is soft massive talc (Piniazkiewicz *et al.*, 1994). Talc has also been referred to as snowgoose, agalite and kerolite. Industrial talc generally refers to products that contain abundant minerals other than talc; cosmetic talc now normally contains >98% talc (Zazenski *et al.*, 1995) but the content may have been lower in the past (Rohl *et al.*, 1976). Pharmaceutical talc contains >99% talc. Talcum powder is cosmetic-grade talc (Zazenski *et al.*, 1995). Pyrophyllite is similar to talc in atomic structure but contains aluminium instead of magnesium ($Al_2Si_4O_{10}(OH)_2$) (Bish & Guthrie, 1993); the two minerals do not occur together in nature, although they have similar industrial applications.

1.1.2   *Structure of the typical mineral*

Chemical formula: $Mg_3Si_4O_{10}(OH)_2$
Molecular weight: 379.26

The original X-ray spectra of talc (Gruner, 1934; Hendricks, 1938) indicated that mineral talc had a monoclinic structure. Later investigations (Ross *et al.*, 1968; Rayner & Brown, 1973) demonstrated that talc is triclinic (Table 1.1). The small deviations from 90° in angle α and angle γ result in the triclinic symmetry. Indexing the X-ray diffraction

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[1] These synonyms and trade names cover talc, materials that contain talc and talc that is contaminated with other minerals as admixtures.

pattern as a monoclinic structure assumes that angles α and γ are each 90° and doubles the magnitude of one of the lattice parameters (parameter 'c' in Table 1.1).

Table 1.1. Lattice parameters and crystallographic axes of talc

Lattice parameters (nm)			Crystallographic axes			System	References
a	b	c	α	β	γ		
0.5255	0.9137	0.9448	90°46′	98°55′	90°00′	Triclinic	Ross *et al.* (1968)
0.5293	0.9179	0.9496	90°57′	98°91′	90°03′	Triclinic	Rayner & Brown (1973)

The structure of talc is characterized by a hexagonal sheet arrangement of silicon–oxygen tetrahedral groups linked in a common plane. Each silicon–oxygen tetrahedron shares three planar oxygen atoms with its neighbouring tetrahedra; the fourth oxygen, the apex of the tetrahedron, is not shared. Two such sheets are orientated so that unshared apical oxygen atoms face each other. The sheets are bonded by magnesium atoms that are coordinated octahedrally by two oxygen atoms from each tetrahedral sheet and two hydroxyl groups. This structural arrangement results in a double-sheet structure in which the valence demands of the constituent atoms are completely satisfied without interlayer cations; these double-sheet units are held together only by weak van der Waal's bonds. The double-sheet units are easily separated by slight forces that result in a perfect cleavage direction in the basal plane (Rohl *et al.*, 1976; Pooley & Rowlands, 1975). The structure of talc is depicted in Figure 1.1 (see cover photo of this Volume).

1.1.3   *Chemical and physical properties of mineral talc*

Hardness: 1 on Mohs' scale
Density: 2.58–2.83
Cleavage: (001) perfect
Colour: Pale to dark green or greenish grey to black; also white, silvery-white, grey, brownish
Luster: Translucent; pearly, greasy or dull
Indices of refraction: Talc is biaxial with α=1.539–1.550, β=1.589–1.594 and γ=1.589–1.600. The indices of refraction increase with iron content. Because β and γ are approximately equal, talc appears to be uniaxial (Deer *et al.*, 1962).
Description: Commonly thin tabular crystals, up to 1 μm in width; talc is usually massive, fine-grained and compact; it also occurs as foliated or fibrous masses or in globular stellate groups. Talc particles are normally thin and plate-like, but the size of the individual plates varies among different bodies of ore. When viewed under the microscope on end, talc platelets may appear as fibres (Cralley *et al.*, 1968). These are not true fibres and should not be confused with asbestiform talc. Asbestiform talc is

Figure 1.1 Schematic structure of talc

From NIMSoffice, http://en.wikipedia.org/wiki/File:Talc.GIF
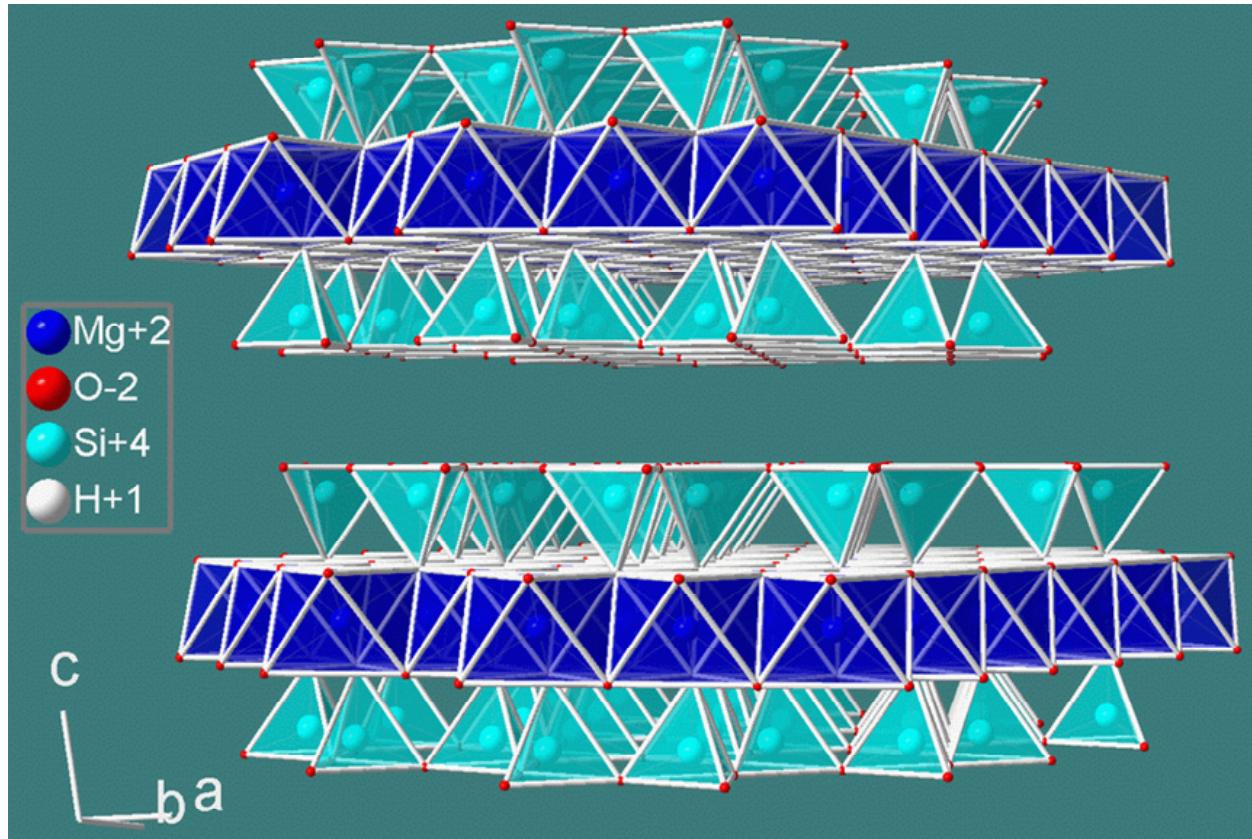
formed when talc plates elongate parallel to the a axis within the plate to form true ribbon-like fibres of talc. These fibres may occur in an asbestiform habit consisting of bundles of narrow fibres randomly oriented around the axis of elongation (c axis). In some deposits, including those in the Gouverneur District of New York State, a small proportion of talc fibres are intergrown on a nanoscale with amphiboles (Stemple & Brindley, 1960; Greenwood, 1998; Wylie *et al.*, 1997).

Chemical composition: The ideal formula is $Mg_3Si_4O_{10}(OH)_2$. When expressed in the standard oxide form, the ideal chemical composition is: 31.9% MgO, 63.4% SiO_2 and 4.8% H_2O (Piniazkiewicz *et al.*, 1994). No talc is ideal, and small amounts of aluminium and iron are common impurities. Aluminium may substitute for both magnesium and silicon; iron(II) and iron(III) may substitute for magnesium. Talc that has almost all magnesium substituted by iron is called minnesotaite and is abundant in the iron formations of Minnesota, USA (Deer *et al.*, 1962). Fluorine is the most common substitution for the hydroxy group (Petit, 2005). Small amounts of nickel, chromium, calcium, potassium, sodium and manganese are also found in the octahedral sites while titanium may substitute for silicon in the tetrahedral site. Table 1.2 provides examples of the variability in the composition of mineral talcs, talc ores and talc products.

Solubility: The solubility of talc has been described in detail by Jurinski and Rimstidt (2001). On the sole basis of dissolution under pulmonary conditions, authors estimated that the maximum residence time in the lung of a 1-μm 'spherical' particle of talc is approximately 8 years. The reader is referred to Section 4 for a detailed description of the kinetics of deposition and clearance.

1.1.4 *Chemical and mineralogical characteristics of talc deposits*

Talc ore deposits are formed from the hydrothermal metasomatism of pre-existing rocks by fluids that contain silicon and/or magnesium. Hydrothermal fluids may be derived from fluids that migrate during retrograde or prograde regional metamorphism or from contact metamorphism that is associated with nearby or distant intrusive igneous rocks. The chemical composition of talc and its associated minerals result from the original rock type, the nature of the hydrothermal alteration and metamorphic history (Harben & Kuzvart, 1996).

The chemical and mineral compositions of talc from various locations are shown in Tables 1.2 and 1.3, respectively.

(a) *Talc derived from mafic and ultramafic rocks*

Talc deposits, the protoliths of which are ultramafic (or mafic) rocks, are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts, such as the Alps, the Appalachians and the Himalayas, and form during the regional metamorphism that accompanies orogenesis. They also occur in Canada (Ontario and Quebec), Egypt, Finland, Germany, Norway, the Russian Federation (Shabry and Miassy),

Table 1.2 Chemical composition (wt%) of selected mineral talcs, talc ores and talc mineral products

Component	Mineral talc[a,b]									Talc ores[c]									
	1	2	3	4	5	6	7	8	9	1[d]	2[d]	3[d]	4[d]	5[e]	6[e]	7[e]	8[e]	9[f]	10[g]
SiO_2	62.61	62.67	62.47	62.16	60.06	60.02	60.88	61.07	51.29	70.8	49.8	44.6	44.8	35.98	59.15	62.65	59.80	54.92	60
TiO_2	–	–	–	–	–	–	0.10	–	0.04	0.07	0.03	0.03	0.06	0.02	–	–	–		
Al_2O_3	–	0.38	0.47	0.88	1.60	1.88	1.98	2.42	0.61	0.69	0.48	0.45	1.20	0.43	0.26	0.31	0.57		0.70
Fe_2O_3	–	0.68	–	–	–	–	0.83	1.49	2.00	0.86	0.29	0.51	0.46	0.65	3.36	1.51	0.05	0.46	2.2
FeO	2.46	0.65	0.79	1.41	1.74	1.51	–	–	33.66	–	–	–	–	5.96	–	–	0.15		
MnO	0.01	–	0.00	–	–	–	–	–	0.12	0.01	0.02	0.03	0.03	0.41	–	–	0.39		
MgO	30.22	29.95	31.76	30.86	30.83	30.39	31.18	29.13	6.26	23.2	19.9	23.2	25.0	32.95	31.34	30.23	27.45	27.20	31
CaO	–	1.35	0.00	–	0.40	1.00	0.14	0.75	0.00	0.07	10.4	14.7	9.98	0.00	0.15	Trace	6.80	5.76	
Na_2O	–	–	–	–	–	–	–	–	0.08	<0.15	<0.15	<0.15	0.59	0.00	–	0.15	–		
K_2O	–	–	–	–	–	–	–	–	0.03	<0.02	0.31	<0.02	0.93	0.00	–	0.05	–		
Loss on ignition										3.99	18.1	16.0	16.1	23.18	6.06	5.14	5.93	10.76	5.80
NiO										–	–	–	–	0.21	–	–	–		
Cr_2O_3														0.18					
H_2O^+	4.72	5.05	4.70	4.92	5.02	5.37	4.98	4.82	5.54										
H_2O^-	–	–	0.06	–	–	0.32	–	–	0.24										

[a] From Deer et al. (1962)

[b] 1, Talc, altered periodotite (Muruhatten, northern Sweden); 2, Talc (Shabrov, Urals, USSR); 3, Talc (Murphy, NC, USA); 4, Light-green talc (Malangen, Norway); 5, Green talc, altered serpentine (Parma district, Apennines, Italy); 6, Black talc, with carbonaceous material derived from a bluish gray rock (Parma, Apennines, Italy); 7, Talc (Mount Fitton, South Australia); 8, Talc, altered tremolite (Yellandu Warangal district, Hyderabad, India); 9, Greenish gray iron talc (minnesotaite) (East Mesabi range, MN, USA)

[c] 1, Talc rock (Alliance Mine, CA, USA); 2, Talc ore (Pleasanton Mine, CA, USA); 3, Talc ore (Talc City, USA); 4, Talc ore (Acme Mine, CA, USA); 5, Vermont talc–magnesite ore (USA); 6, Flotation product (Johnson, VT, USA); 7, Steatite (Yellowstone Mine, MT, <USA); 8, Average ore (Talcville, NY, USA); 9, Texas talc (USA); 10, FINNTALC M30

[d] From Van Gosen et al. (2004)

[e] From Chidester et al. (1964)

[f] From Pence (1955)

[g] From Mondo Minerals (2005)

southern Spain and the USA (Arkansas, California and Texas) (Piniazkiewicz *et al.*, 1994; Harben & Kuzvart, 1996). These deposits may contain trace amounts of nickel, cobalt and chromium that are derived from their ultramafic protolith. One major talc deposit in eastern USA contains substantial amounts of nickel (up to 0.2%; Rohl *et al.*, 1976). Nickel-substituted talc is also associated with serpentine bodies, at up to 0.5% by weight (Pooley & Rowlands, 1975); pentlandite has been reported in talc from Finland from which it is recovered by flotation (Harben & Kuzvart, 1996). Quartz is uncommon in talc that has mafic or ultramafic protoliths and the fluorine content is generally low (Ross *et al.*, 1968). Chlorite and amphiboles are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history. A small amount of amphibole asbestos is associated with this type of talc deposit at Soapstone Ridge, GA (USA) and anthophyllite asbestos is abundant in the vicinity of the talc at Dadeville, AL (USA) (Van Gosen *et al.*, 2004). In a few deposits, the parent was mafic rock (Virginia (Schuyler), Georgia and Egypt) (Harben & Kuzvart, 1996).

Table 1.3. Mineral composition (wt%) of talc from various locations

Mineral	Montana	Vermont	North Carolina	New York[a]	California	France
Talc	90–95	80–92	80–92	35–60	85–90	70–90
Tremolite	–	–	–	30–55	0–12	–
Anthophylite	–	–	0–5	3–10	–	–
Serpentine	–	–	–	2–5	–	–
Quartz	<1	<1	1–3	1–3	<1	<1
Chlorite	2–4	2–4	5–7	–	–	10–30
Dolomite	1–3	1–3	2–4	0–2	0–3	–
Calcite	–	–	–	1–2	–	–
Magnesite	0–5	0–5	–	1–3	–	–

From Harben & Kuzvart (1996)
[a] Gouverneur District

(b)   Talc derived from magnesium carbonates

Talc deposits formed from the alteration of carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized: (i) those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite (Australia (Mount Seabrook and Three Springs), China, India, Republic of Korea, the Russian Federation (Onot), northern Spain (Respina) and the USA (Alabama (Winterboro), California (Talc City), Montana (Yellowstone), Washington (Metaline Falls) and West Texas); and (ii) those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks (Austria (Leogen), Brazil (Brumado), Canada

(Madoc), France (Trimouns), Germany (Wunsiedel), Italy (Chisone Valley), the Russian Federation (Krasnoyarsk), Slovakia (Gemerska Poloma), Spain and the USA (Chatsworth, GA, Death Valley–Kingston Range, CA, Murphy Marble belt, NC, and New York). In a few of these deposits, including the large deposit at Trimouns, France, the talc may be classified as being derived from alumino-silicate rocks (Harben & Kuzvart, 1996; Luzenac, 2004).

Talc derived from magnesium carbonate may contain quartz. Van Gosen *et al.* (2004) suggested that, among the first group, only those that are formed by hydrothermal alteration of dolomites that are in direct contact with igneous bodies are probably accompanied by amphiboles (e.g. Death Valley, CA, USA) and that hydrothermal deposits in carbonates that are formed by relatively low-temperature fluids derived from distant igneous bodies contain no or only very minor amounts of amphibole (Talc City, CA, Southwestern Montana and Allamoore, TX, USA). In some deposits in the second group, amphiboles may be very abundant, especially those formed during high-temperature regional metamorphism of impure dolomites. In the Gouverneur District New York State, for example, non-asbestiform tremolite comprises between 30 and 70% of the talc product (Harben & Kuzvart, 1996).

Gouverneur District New York State talc that is currently marketed under the trade name Nytal is a unique industrial mineral product that can readily be distinguished from all other commercially available industrial talcs based on its mineral content. Nytal 100, for example, contains 30–50% tremolite, 20–40% talc, 20–30% serpentine, 2–10% anthophyllite and 0.14% quartz (R.T. Vanderbilt Company, 2000). The tremolite, anthophyllite and serpentine occur as mineral fragments and not as asbestiform fibres. Tremolite from this deposit has been characterized in detail (Campbell *et al.*, 1980). Nytal also contains asbestiform fibres of talc and talc intergrown on a nanoscale with amphibole (Wylie *et al.*, 1997). Wylie *et al.* (1997) estimated that the abundance of particles that are longer than 5 μm and have an aspect ratio of 3:1 or greater in sample FD14 (identified as a commercial talc product from New York State) is $0.8 \times 10^3/\mu g$; 62% of these particles were identified as talc, 24% as fragments of tremolite plus a small amount of anthophyllite and 14% as talc intergrown with anthophyllite. Products from other mines in this district before 1964 contained different proportions of anthophyllite and tremolite, which may be asbestiform (Chidester *et al.*, 1964).

(c)   Minerals associated with talc

Because talc deposits are formed from different protoliths under many different geological conditions, each talc deposit has a combination of mineralogy and mineral habit that is distinctive and, in many cases, unique. The most common minerals found in talc products include chlorite, magnesite, dolomite, tremolite, anthophyllite, serpentine and quartz. However, many other minerals have been reported; these are given in Table 1.4 (Pooley & Rowlands, 1975; Piniazkiewicz *et al.*, 1994; Harben & Kuzvart, 1996). Some of these minerals are beneficial to certain applications such as tremolite in ceramics.

TALC   285

Table 1.4. Minerals commonly associated with talc

Mineral group	Name	Ideal formula
Carbonate	Dolomite	$(Ca,Mg)CO_3$
	Magnesite	$MgCO_3$
	Breunnerite	$(Mg,Fe)CO_3$
	Calcite	$CaCO_3$
	Siderite	$FeCO_3$
	Ankerite	$Ca(Fe,Mg,Mn)(CO_3)_2$
Phyllosilicates	Chlorite	$(Mg,Al,Fe)_{12}(Si,Al)_8O_{20}(OH)_{16}$
	Serpentine (lizardite and antigorite)	$Mg_3Si_2O_5(OH)_4$
	Phlogopite (mica)	$K_2(Mg,Fe)_6Si_6Al_2O_{20}(OH)_4$
	Sepiolite	$Mg_8Si_{12}O_{30}(OH)_4(H_2O)_4$
Amphibole[a]	Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
	Anthophyllite	$(Mg,Fe)_7 Si_8O_{22}(OH)_2$
	Actinolite	$Ca_2(Mg,Fe)_5 Si_8O_{22}(OH)_2$
Tectosilicates	Quartz	SiO_2
	Feldspar	$(K,Na)AlSi_3O_8$
Oxides	Magnetite	Fe_3O_4
	Ilmenite	$FeTi O_3$
	Manganese oxide	MnO_2
	Rutile	$Ti O_2$
Sufides	Pyrite	FeS_2
	Pyrrhotite	FeS
	Pentlandite	$(Fe,Ni)_9S_8$
Other minerals	Tourmaline[b]	$NaFe_3Al_6(BO_3)_3Si_6O_{18}(OH)_3(OH)$
	Graphite	C

Compiled by the Working Group from Pooley & Rowlands (1975); Piniazkiewicz *et al*. (1994);
Harben & Kuzvart (1996)
[a] See Leake *et al*. (1997) for precise nomenclature and chemical composition of the amphibole
group.
[b] This is the formula for one member of the tourmaline group; chemistry is highly variable.

(d)   Chemical composition of talc ore

   The variability in the chemical composition of talc ore, talc mineral products and talc
rock primarily reflects their mineral composition (see Table 1.2).

1.1.5   *Processing of talc ores and composition of talc products*

Talc ores may be processed by a variety of techniques that include selective mining, hand sorting and milling by roller mills, hammer mills, ball mills, fluid energy mills and jet mills and are classified and separated from other minerals by froth flotation or magnetic separation. Some may be treated with acid and calcined. The particle sizes of talc and the abundance of the associated minerals are determined by characteristics of the ore, methods of processing, and the duration of grinding. Grinding breaks the talc platelets along (001) and disaggregates the particles; prolonged grinding may destroy the crystallinity (Sanchez-Soto *et al.*, 1997; Zbik & Smart, 2005). Roller mills tend to preserve the platy structure and different types of milling affect properties such as flatness, surface roughness, roundness, width and elongation (Yekeler *et al.*, 2004). Talc particles are platy, and sizes reflect the dimension parallel to the plate; data are not available on the thinness of the plates.

Talc products also vary in particle size; median sizes range from ~1 to >20 μm and top sizes range from <10 to >100 μm. The most common designations for fineness are based on US Sieve Series and Tyler equivalence and include 200 mesh (95–98% <74 μm), 325 mesh (95–99% <44 μm) and 400 mesh (95–99% <37 μm) (Zazenski *et al.*, 1995).

Talc products that contain >95% mineral talc are used in cosmetics, baby powder, pharmaceuticals, steatite ceramics, pitch control in the paper industry and as a filler in rubber. Today, the talc in baby powders is >99% 200 mesh (Zazenski *et al.*, 1995). Talc products that contain between 75 and 95% mineral talc are used in paper fillers, reinforced plastics, paint, ceramics and dusting compounds for rubber. Lower-purity talc is used in roofing material, patching compounds, flooring and fertilizers (Piniazkiewicz *et al.*, 1994). Particle sizes, colour and nature of associated minerals also vary among these applications.

1.1.6   *Analysis*

        (a)   *Analysis of bulk samples*

Talc can be identified from its optical properties by polarized light microscopy and oil immersion, from its X-ray or electron diffraction pattern, from its chemical composition and from differential thermal analysis/thermal gravimetric analysis. Chlorite has similar optical properties. Talc platelets on end and talc intergrown with amphibole in fibrous talc have complex electron diffraction patterns that may resemble other silicates, including amphiboles (Stemple & Brindley, 1960) and sepiolite (Germine, 1987), unless carefully indexed. Anthophyllite and sepiolite have chemical compositions that are very similar to talc and require quantitative chemical analysis to differentiate them, including the use of well characterized standards in the case of dispersive X-ray analysis used in conjunction with electron microscopy. Identification of mixed mineral assemblages by X-ray

TALC   287

diffraction may be difficult because of pattern overlap (Krause, 1977) and X-ray diffraction cannot distinguish asbestiform minerals from other habits.

Particle size distributions that are determined by settling underestimate the abundance of larger particles and overestimate the number of smaller particles because the platy structure results in longer settling times for talc compared with spherically shaped particles of equivalent size. Computer-controlled scanning electron microscopy has been used to provide a more accurate size distribution. Determination of the respirable fraction of bulk materials by these two methods differs significantly (Zazenski *et al.*, 1995).

(b)   *Analysis of exposure*

The standard methods for the analysis of airborne exposures in an occupational setting where asbestos is known to be present include those of the Health and Safety Executive (1995) and the Occupational Safety and Health Administration (2005). These methods were designed to provide an index of exposure since they count only particles longer than 5 μm with a length-to-width ratio of 3:1 or more that are visible by phase-contrast microscopy. They do not determine the mineral identity of the particles counted. In a mining environment where many minerals form elongated fragments, the results of fibre counts can be difficult to interpret. In bulk samples of talcum products, for example, Cralley *et al.* (1968) reported that particles longer than 5 μm with a 3:1 aspect ratio in 22 talcum products represented 19% of the particles, which were predominantly talc.

Conversion of fibre counts to gravimetrically based exposure metrics is complicated as this will depend on the particle size. Oestenstad *et al.* (2002) adjusted million particles per cubic foot (mppcf) to milligrams per cubic metre (mg/m^3) using the following regression equation:

$$\ln (mg/m3) = \ln (mppcf) \times 0.62 - 1.20$$

All gravimetric measurements to monitor exposure to talc in occupational settings are taken from samples of respirable dust particles. The reader is referred to the Glossary and the monograph on carbon black for further details.

1.2   Production and use

1.2.1   *Production*

Talc deposits result from the transformation of existing rocks under hydrothermal activity and are classified according to the parent rock from which they derive. There are three broad types of talc deposit of commercial significance (Luzenac, 2004; EUROTALC, 2005; Industrial Minerals Association-Europe, 2005): (i) talc derived from mafic and ultramafic rocks, which provides about 40% of talc supplies; the crude ore is usually grey and, to be commercially viable, may be upgraded to improve the mineralogy and whiteness (generally by flotation); (ii) talc derived from magnesium carbonates, which provides >50% of world production; and (iii) talc derived from alumino-silicate

rocks, from which about 10% of world production is mined, and which is sometimes found in combination with deposits of magnesium carbonate; the crude ore is generally grey due to the presence of chlorite, but no upgrading is necessary as chlorite performs adequately in the applications of interest.

This wide diversity of origins and types of deposit naturally gives rise to a wide variety of ores and product grades that differ according to their mineralogical composition, colour and crystalline structure (microcrystalline or lamellar) (Luzenac, 2004; EUROTALC, 2005; Industrial Minerals Association-Europe, 2005).

World production of talc and pyrophyllite in both 2003 and 2004 was estimated to be 8.3 million tonnes. Of the total production, approximately 2.15 million tonnes were confirmed to be used for talc production in both 2003 and 2004. China was the leading producer of talc in the world, followed by the USA, India, Brazil (crude) and France (crude). The Republic of Korea was the leading producer of pyrophyllite, followed by Japan and Brazil. Brazil, China, France, India, Japan, the Republic of Korea and the USA produced 84% of talc and pyrophyllite in the world (Table 1.5) (Virta, 2004).

Table 1.5. World production of talc (in tonnes unless otherwise specified)[a,b]

Country	2000	2001	2002	2003	2004
Argentina	6730	1665	1643	1759	1800
Australia[c]	178 545	173 446	173 741	174 000	173 000
Austria (crude+so)[d]	130 000[e]	140 000	135 000	135 000	135 000
Bhutan[d]	3700	3800	3900	3900	3900
Brazil (crude)	300 000	397 000	348 000	365 000	370 000
Brazil (marketable product)[f]	7049	6300	5617	5593	5600
Canada (t+p+so)	86 000	90 000	90 000	90 000	90 000
Chile	2421	4177	3537	4374	4400
China (unspecified)[d]	3 500 000	3 500 000	2 500 000	3 000 000	3 000 000
Colombia (t+p+so)[d]	15 000	15 000	15 000	15 000	15 000
Egypt (t+p+so+st)[d]	40 000	40 000	40 000	40 000	40 000
France (crude)[d]	350 000	350 000	350 000	350 000	350 000
Germany (marketable+st+t)[d]	8000	10 000	10 000	10 000	10 000
Hungary[d]	500	500	500	500	500
India (st)	545 000	546 000	550 000	552 000	550 000
Iran[d,g]	25 000	25 000	25 000	25 000	30 000
Italy (t+st)[d]	140 000	140 000	140 000	140 000	140 000
Japan	50 000	45 000	40 000	40 000	35 000
Macedonia	562	557	550	550	600
Mexico	20 569	77 650	111 621	114 870	115 000
Morocco	12 522	27 246	39 612	1959	2000
Nepal[h]	5852	3923	2621	2500	2400
Norway (t+so+st)[d]	27 000	27 000	28 000	28 000	28 000
North Korea (unspecified)[d]	120 000	120 000	110 000	110 000	110 000
Paraguay (t+p+so)[d]	200	200	200	200	200
Peru	9668	11 165	10 685	10 791	10 000
Portugal[d]	8200	8200	8200	8200	8000
Republic of Korea	11 344	47 712	37 863	47 911	48 000
Romania	7850	7270	7292	10 082	10 000
Russia[d]	100 000	100 000	100 000	100 000	100 000

TALC   289

Table 1.5 (contd)

Country	2000	2001	2002	2003	2004
Slovakia	1800	2600	2290	1000	1500
South Africa	5600	3218	2511	4472	12 065[e]
Spain (t+st)[d]	100 000	100 000	100 000	100 000	100 000
Sweden (t+so)	20 000	15 000	15 000	15 000	14 000
Taiwan	–	130	27	466	411[e]
Thailand	7390	6838	1702	8501	8500
United Kingdom (t+p+so)[d]	5000	5000	5000	5000	5000
USA	851 000	863 000	828 000	840 000	857 000[e]
Uruguay (t+p+so)	2903	1694	1700	1700	1700
Zimbabwe	989	1273	911	196	–[e]

From Virta (2004)

p, pyrophyllite; so, soapstone; st, steatite; t, talc

[a] World totals; data from the USA and estimated data are rounded to no more than three significant digits; may not add to totals shown.

[b] Table includes data available through to April 19 2005.

[c] Data based on Australian fiscal year ending 30 June of the year stated.

[d] estimated

[e] Reported figure

[f] Direct sales and/or beneficiated (marketable product)

[g] Data based on Iranian fiscal year beginning 21 March of the year stated

[h] Data based on Nepalese fiscal year beginning mid-July of the year stated

1.2.2   *Use*

The properties of mineral talc (platyness, softness, hydrophobicity, organophilicity and inertness) and the mineralogical composition of talc products govern their specific applications in many industries and processes including paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, cosmetics and pharmaceuticals. The principal technical applications of talc in commercial products are as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, strengthening and smoothing filler and absorbent (Industrial Minerals Association-Europe, 2005).

(a)   End-use categories

(i)   *Agriculture and food*

Talc is used as an anti-caking agent, dispersing agent and die lubricant in animal feed and fertilizers. In premixes and agricultural chemicals, it is used as an inert carrier. Talc is also used as an anti-stick coating agent in several foods and as a processing aid in the production of olive oil. (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

Agricultural chemicals. Talc is a functional carrier in agricultural products that offers very low moisture equilibrium, relative hydrophobicity and chemical inertness. Costs are reduced by extending expensive chemicals and improving the dispersion and flow of

active ingredients. Talc is appropriate for garden dusts, flea and tick powders, seed treatments and biocides (Luzenac, 2004).

Anti-caking and homogenization. Talc improves the flowability of difficult raw materials, e.g. oilseed meal and finished products, and feeds with high loads of sticky ingredients such as molasses, oil, fatty products, urea, milk powder and sugar. The smooth and flat lamellae of talc cover each particle and help them to flow freely. As they are naturally water-repellent, talc particles form a barrier when they envelop other particles and reduce the evaporation and uptake of water within the product mass. Talc platelets help different constituents to blend more easily and facilitate the dispersion of sticky ingredients (Luzenac, 2004).

Die lubricant. Talc is a cost-effective die lubricant especially for high-fibre, high-sugar and high-mineral formulations and pelleted feeds (Luzenac, 2004).

Fertilizers. Talc is used as an anti-caking agent in both prilled (pelleted or granulated) ammonium nitrate and granular fertilizers. Talc particles reduce the absorption of moisture and prevent the formation of hydrate bridges, which enables longer storage periods. In Europe, amine-coated talcs are marketed with enhanced adhesion properties that enable the amine contents to be reduced and result in lower dust levels and less environmental impact (Luzenac, 2004).

Foods. Talc is an effective anti-stick coating agent that is used in several foods, such as chewing gum, candies and cured meats (Luzenac, 2004).

Processing of olive oil. In the production of olive oil, talc acts as a natural processing aid that improves extraction and increases the yield of virgin olive oil (Luzenac, 2004).

Premixes. Talc is used as an inert carrier for active premix ingredients. Certain talc grades have been specifically designed for dust-free, high-specification requirements (Luzenac, 2004).

(ii)   *Ceramics*

Talc imparts a wide range of properties to floor and wall tiles and sanitary ware, tableware, refractory goods and technical ceramic products. In traditional building ceramics (tiles and sanitary ware), it is used essentially as a flux to enable firing temperatures and cycles to be reduced. In refractory applications, talcs that are rich in chlorite are used to improve thermal shock resistance. Talcs with a microcrystalline form are the most appropriate for steatite ceramics. During firing, the talc is transformed into enstatite, which possesses electro-insulating properties. Talcs with a very low iron content are particularly suitable for use in frit, engobe [underglaze] and glaze compositions (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(iii)   *Coatings*

Talcs confer several properties on coatings. In interior and exterior decorative paints, they act as extenders to improve hiding power and the efficiency of titanium dioxide. The lamellar platelets of talc make paint easier to apply and improve cracking resistance and sagging, and also enhance matting. In anti-corrosion primers, talcs are used to improve

resistance to corrosion and adhesion of the paint. They are also used in inks, jointing compounds, putties and adhesives (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(iv)   *Paper*

Talcs are used in both uncoated and coated rotogravure papers in which they improve printability, reduce surface friction and enhance handling characteristics. They also improve mattness and reduce ink scuff on offset papers. When used as pitch-control agents, talcs 'clean' the papermaking process by adsorbing any sticky resinous particles in the pulp onto their platy surfaces, and thereby prevent the agglomeration and deposition of these on the felts and calenders. In contrast to chemical pitch-control products that pollute the process water, talc is removed with the pulp, which enables the papermaker to operate more easily in a closed circuit. In specialty papers such as coloured papers or labels, talcs help to improve quality and productivity (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(v)   *Personal care*

As it is soft to the touch and inert, talc has been valued for centuries as a body powder. Today, it also plays an important role in many cosmetic products, including products for feminine hygiene and baby powders, and provides the silkiness in blushes, powder compacts and eye shadows, the transparency of foundations and the sheen of beauty creams. In pharmaceutical products, talc is an important excipient that is used as a glidant, lubricant and diluent. Soap manufacturers also use talc to enhance the performance of skin care products (Luzenac, 2004; Industrial Minerals Association-Europe, 2005). Table 1.6 presents information on levels of talc in cosmetic products in the USA and Table 1.7 gives the composition of some examples of products that are used for body care.

(vi)   *Plastics*

Talcs impart a variety of properties to polypropylene, such as greater stiffness and improved dimensional stability in automotive parts, household appliances and white goods. Advanced milling technology is required to obtain the finest talcs without diminishing the reinforcing power of their lamellar structure. Talcs are also used for the anti-blocking of linear low-density polyethylene and as a nucleating agent in semicrystalline polymers. In polypropylene that is used in food packaging applications, talc is a highly effective reinforcing filler. The grades of talc used for this purpose include calcined, surface-treated, ultrafine grind and high aspect ratio (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

(vii)   *Roofing*

Talc is a high-performance product that is used to back surfacing asphalt shingles. The use of talc is even more important in the growing market for laminated shingles in

which handling is more complex, wear and tear on machinery is greater, cutting is doubled and adhesion of the interlayer is critical (Luzenac, 2004).

Table 1.6. The number of cosmetic products in the Cosmetics and Toiletries Formulations Database in the USA that contain talc or talcum

Product categories	No. of products
Antiperspirants and deodorants	22
Baby products	6
Bath and shower products	2
Beauty aids[a]	184
Creams	14
Hair care products	1
Lipsticks	5
Lotions	1
Shampoos	1
Shaving products	2
Sun care products	3
Miscellaneous[b]	8

Compiled by the Working Group from Flick (2005)
[a] Beauty aids includes aerosol talc products, face masks, foundations, body oils, make-up bases, concealers, blushes, body powders, rouge, make-up, compact powders, eye shadows, dusting powders, eyebrow pencils, pressed powder products, face powders, mascaras, liquid talc products and powder cleansers
[b] Miscellaneous includes aerosol talc foams, wound ointments, foundations with extracts, foot powders, liquid foundations and sport tints

(viii) Rubber

Talcs reduce the viscosity of rubber compounds and thereby facilitate the processing of moulded parts. They also improve the quality of extrudates, which increases production rates and enhances the resistance to ultraviolet (UV) radiation of exterior parts such as automotive profiles. In sealants and gaskets, they provide compression resistance, while in pharmaceutical stoppers, they create a barrier against liquids. Talcs are used as insulators in cables and as processing aids in tyre manufacture (Luzenac, 2004; Industrial Minerals Association-Europe, 2005).

TALC   293

Table 1.7. Composition of some products used for body care

Product	Wt% talc	Other components	Wt% other components
Dusting powder	97.7	Perfume oil	0.8
		GLUCAM P-20	1.5
		Preservative	q.s.
Dusting powder	91.6	Magnesium carbonate	3.0
		Zinc stearate	3.0
		Triclosan	0.2
		Perfume oil	0.7
		GLUCAM P-20	1.5
		Preservative	q.s.
Velvety dusting powder	77.4	Aluminum starch, Octenyl succinate	20.0
		Zinc stearate	2.0
		Methylparaben	0.10
		Propylparaben	0.10
		Germall II	0.20
		Fragrance	0.20
Face and body powder	89.30	Boron nitride	10.00
		Methylparaben	0.15
		Propylparaben	0.20
		Imidazolidinyl urea	0.05
		Iron oxide (yellow)	0.20
		Iron oxide (red)	0.10
Baby powder	72	DYNASAN 114	2.0
		Magnesium stearate	8.0
		Kaolin	18.0
After-bath talc	92.5	Perfume oil	5.0
		PPG-20 methyl glucose ether	1.50
		Macadamia nut oil	1.00
Body powder	4.0	Boron nitride	5.0
		Silica	2.5
		Starch	30.2
		Kaolin	10.0
		Magnesium stearate	1.00
		Bentone 38/Quaternium18, Hectorite	1.0
		Isopropyl myristate	6.0
		Perfume	1.8
		Pigments	q.s

Table 1.7 (contd)

Product	Wt% talc	Other components	Wt% other components
Powder for babies and children	20.0	Kaolin	20.0
		Rice starch	51.0
		Zinc stearate	5.0
		Eutanol G	2.0
		Lanette O	2.0
Dispersing bath powder	0	Kukui nut oil	1.0
		Phenyl trimethicone	1.0
		Cyclomethicone	2.0
		Fragrance	1.5
		Ethoxydiglycol	2.0
		Oleth-2	2.50
		Oleamidopropyl PG, dimonium chlorite	2.0
		Topopheryl acetate (Vitamin E)	0.50
		Cornstarch	86.00
		Silica	1.50
Body powder	0	Zinc stearate	5.0
		Zinc oxide	5.0
		Magnesium carbonate	15.0
		Kaopolite TLC	75.0
Talc-free body powder	0	Cornstarch	88.45
		Kaolin	5.0
		Mica	2.0
		Titanium dioxide	2.0
		Red mica and titanium dioxide	0.25
		Tapioca starch	2.0
		Methylparaben	0.10
		Propylparaben	0.05
		Imidazolinidyl urea	0.15

From Flick (2005)
The Working Group was aware that these data are not representative of all products
q.s., quantum satis (sufficient quantity)

(ix)   *Wastewater treatment*

Specialty talc can improve the performance of biological wastewater treatment plants.
The talc particles ballast the flocs of bacteria and accelerate their sedimentation (Industrial
Minerals Association-Europe, 2005).

(x)   *Other*

Talc is used as an anti-sticking agent to powder moulds in foundries and in the manufacture of pharmaceuticals and rubber or on conveyor belts that carry foodstuffs. It is also used in other products, such as condoms and surgery gloves. Particle-wood boards (chip boards) are powdered with talc to avoid sticking when stockpiled. Talcs are also used as smooth fillers, for example in the 'lead' of colouring pencils and in putties (where it can be the major component) (Industrial Minerals Association-Europe, 2005).

Talc had been used as a sclerosing agent in the pleural space for the treatment of spontaneous pneumothoraces. Talc is also used for pleurodesis in the treatment of malignant pleural effusions (Dresler *et al.*, 2005). The products used for these purposes contain 95% talc and 5% chlorite and dolomite.

(b)   *Use patterns*

The worldwide use pattern for talc in 2000 was: paper, 30%; ceramics, 28%; refractories, 11%; plastics, 6%; a filler or pigment in paints, 5%; roofing, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (art sculpture, asphalt filler, autobody filler, construction caulks, agriculture and food, flooring and joint compounds) (Roskill Information Services Ltd, 2003). The use pattern for talc in the USA in 2004 was: ceramics, 32%; paints, 19%; paper, 16%; roofing, 6%; plastics, 4%; rubber, 3%; cosmetics, 1%; and other, 19% (Virta, 2004). The use of talc in cosmetics in the USA decreased from 34 000 tonnes in 1993 to 5000 tonnes in 2004 (Virta, 2004).

The estimated world consumption of talc by geographical region in 2000 was: Asia, 43%; western Europe, 19%; North and central America, 17%; South America, 8%; Indian subcontinent and Middle East, 8%; Africa, 2%; eastern Europe and Commonwealth of Independent States countries, 2%; and Australia and New Zealand, 1% (Roskill Information Services Ltd, 2003).

1.3   Occurrence and exposure

1.3.1   *Natural occurrence*

Talc is found in small amounts in metamorphic mafic and ultramafic rocks and in carbonates. These metamorphic rocks crop out in mountain belts such as the Alps, the Appalachians and the Himalayas and in ancient continental shields such as the Canadian shield in New York and Canada.

The occurrence of talc deposits of commercial importance is described extensively in Section 1.1.4.

1.3.2   *Occupational exposure*

Exposure to talc dust occurs during its mining, crushing, separating, bagging and loading and in various industries that use talc (see Section 1.2.2). This section reviews

exposure to talc during its mining and milling, other than that from the Gouverneur District New York State mines, and in user industries, whenever this information is available. Exposure to talc is also described, where possible, for those industries in which epidemiological studies have been carried out in relation to the occurrence of cancer.

(a)   Mining and milling

Before the 1970s, exposure measurements were made by collecting particles in an impinger and counting them by optical microscopy. Concentrations were thus expressed as million particles per cubic foot of air (mppcf). More recent studies have described levels of exposure to dust that were assessed using gravimetric measurement techniques.

Table 1.8 describes studies of exposure to talc in mines and mills. In Georgia, USA, average exposures to dust were 1440 mppcf (~50 854 particles/cm^3) for miners who used jackhammer drills and 52 mppcf (~1836 particles/cm^3) for millers. The talc was reported to contain 45% tremolite and 45% talc, with little or no quartz (Dreessen, 1933). Average dust concentrations in a talc mine were reported to range from 32 to 855 mppcf (~1130 to 30 195 particles/cm^3; six samples), whereas those in mills ranged from 17 to 1672 mppcf (~600 to 59 000 particles/cm^3; 14 samples). The dust was reported to contain 70% talc, 20–30% dolomite and 10% tremolite, and no quartz except for occasional fragments; its morphology was described as 'bladed crystals'. Highest exposures to dust occurred during bagging operations (Dreessen & DallaValle, 1935).

Concentrations of respirable dust in mass samples from three Vermont talc mines and mills surveyed in 1975–76 are given in Table 1.9. Geometric mean exposures to respirable dust ranged from 0.5 to 5.1 mg/m^3 in the mines and from 0.5 to 2.9 mg/m^3 in the mills; however, exposures in the mills were generally higher than those in the mines. Optical fibre counts as high as 60 fibres/cm^3 were reported. Subsequent analyses of these samples by scanning electron microscopy showed that they consisted of rolled talc and elongated talc particles. X-Ray diffraction analyses of bulk samples from these mines and mills showed that talc and magnesite were the major (20–100%) mineral components, chlorite and dolomite were minor (5–20%) components and calcite, quartz, biotite, ankerite, chromite, phlogopite and oligoclase were present in small amounts (<5%). Trace amounts of quartz were found in 15% of the samples (Boundy *et al.*, 1979). Dust from one closed mine was reported to contain tremolite microinclusions, but its fibrosity was not documented (Selevan *et al.*, 1979).

A cross-sectional study of occupational exposures in talc mines and mills in the USA was conducted by the National Institute for Occupational Safety and Health; the results are summarized in Table 1.10. Bulk samples from each region were analysed by transmission electron microscopy: no fibre was found in any sample of Montana talc; fibrous tremolite and antigorite were reported in Texan talcs (0.5–3.0 μm in diameter, 4–30 μm in length); and talcs from North Carolina contained particles with length:diameter ratios as high as 100:1, with some <0.1 μm in diameter (Greife, 1980; Gamble *et al.*, 1982). Van Gosen *et al.* (2004) recently reported that the Texan talc contained little or no amphibole.

Table 1.8. Studies of occupational exposures in talc mines and mills

Reference	Location of talc deposit	Date of exposure measurements	Method of measurement	Other minerals present
Dreessen (1933)	Georgia, USA	Pre-1933	Impinger	Tremolite
Dreessen & DallaValle (1935)	Georgia, USA	Pre-1935	Impinger	Tremolite, dolomite
Rubino *et al.* (1976); Coggiola *et al.* (2003)	Piedmont, Italy	1946–95	–	Quartz (radon, diesel exhaust)
Rubino *et al.* (1976)	Piedmont, Italy	1920–75	Impinger	Small amounts of tremolite
Boundy *et al.* (1979)	Vermont, USA	1975–76	Optical and electron microscopy fibre counts	Dolomite, calcite, magnesite, chlorite, traces of other minerals
Greife (1980); Gamble e*t al.* (1982)	Montana, Texas and North Carolina, USA	1977–80	Gravimetric	Varied by location studied
Wild *et al.* (1995, 2002)	France, Austria	1986–92	Gravimetric (CIP personal sampler)	Quartz: France, <3%; Austria, <4%

CIP, capteur individuel de poussière [personal dust sampler]

Table 1.9. Concentrations (mg/m³) of respirable dust in Vermont talc mines and mills

Company	Area	Summer 1975		Winter 1976	
		No. of samples	Geometric mean (mg/m³)	No. of samples	Geometric mean (mg/m³)
A	Underground mine	18	0.6	16	0.5
	Mill (1st shift)	4	1.7	13	1.7
	Mill (2nd shift)	6	0.5	3	1.5
B	Underground mine	15	1.5	23	0.9
	Mill (1st shift)	22	1.8	42	1.8
	Mill (2nd shift)	12	2.9	16	1.9
C	Underground mine	12	0.5	19	0.7
	Walk-in mine	7	1.2		
	Walk-in mine			6	1.7
	Open-pit mine	2	5.1	–	–
	Mill No. 1 (1st shift)	12	0.9	20	1.1
	Mill No. 1 (3rd shift)	3	0.8	4	1.4
	Mill No. 2 (1st shift)	11	1.0	8	0.5
	Mill No. 2 (2nd shift)	13	0.8	3	1.1

From Boundy *et al*. (1979)

Table 1.10. Concentrations of respirable dust in 275 samples from talc mines and mills located in Montana, Texas and North Carolina, USA

Samples	Geometric mean (mg/m³)		
	Montana	Texas	North Carolina
From mines	0.66 (0.47–0.92)[a]	0.45 (0.18–0.71)	0.14 (0.07–0.31)
From mills	1.1 (0.85–1.41)	1.56 (0.96–2.54)	0.26 (1.13–0.51)
Bulk talc samples (% free silica)	<0.8	2.23	1.45

Adapted from Greife (1980); Gamble *et al*. (1982)
[a] In parentheses, 95% frequency interval

Analysis of 362 personal samples of respirable dust collected over a full shift from talc mines and mills by the Mine Safety and Health Administration in the USA showed the median dust exposure to be 1.20 mg/m³; 90% of all exposures were <2.78 mg/m³ (National Institute for Occupational Safety and Health, 1979).

Before the adoption of technical preventive measures in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf [~28 250 particles/cm^3] in the mines and 25 mppcf [~883 particles/cm^3] in the mills. Exposures in both areas were reduced to less than 10 mppcf [~353 particles/cm^3] after 1965 when improved ventilation techniques and wet drilling procedures were introduced. Mineralogical analyses of the footwall rocks demonstrated that they contained quartz, muscovite, chlorite, garnet, calcite, magnesite and small quantities of other minerals. In a few specimens of footwall rocks, a small amount of tremolite was detected, but no other type of amphibole or chrysotile. Talc specimens from these mines were found very commonly to contain chlorite, but no amphibole or chrysotile minerals. The quartz content of powdered talc specimens was generally below the detection limits of X-ray diffraction (Rubino *et al.*, 1976). In recent years, the mean exposure to respirable dust was 1.1 mg/m^3 (range, 0.5–2.5 mg/m^3), while the mean exposure to talc alone was 1.0 mg/m^3 (range, 0.3–2.0 mg/m^3). The authors stated that there was a remarkable difference in the amount of quartz in air dust in mines and mills and within jobs in the mine between drilling and other occupations. This was mainly due to the high content of quartz in footwall rocks, rather than to the absence of quartz particles in talc minerals (Coggiola *et al.*, 2003). [The Working Group noted that the analytical methods were not described in detail and the mineral habit of the tremolite was not documented.]

Wild *et al.* (1995) reported on a survey of the respiratory health of workers in a French talc producing factory. At this quarry, crude talc was extracted and transported directly to the mill using an overhead cable. The extracted ore consisted of a mixture of talc, chlorite, some dolomite (<3%), occasionally quartz (<3%) and traces of calcite, apatite, pyrite and mica. Amphiboles were not detected. A total of 1440 personal samples were taken between 1986 and 1991. The mean levels of exposure to respirable dust ranged from 0.5 mg/m^3 for secretaries, managerial staff and outdoor workers who handled the railway wagons to 15 mg/m^3 for site cleaning staff. In 1991, only one exposure group of four maintenance workers was estimated to have a mean exposure in excess of 5 mg/m^3. However, the probability of exceeding an exposure level of 5 mg/m^3 was more than 10% for most maintenance and some production workers. This was explained by the high variability of exposure among maintenance workers; eight of 10 groups of workers in the maintenance workshop had geometric standard deviations >3. Exposure was found to be more homogeneous among the production workers. The authors claimed that the introduction of centralized aspiration devices and new working procedures had resulted in lower levels of exposure. Mean levels of exposure in the in the past were estimated to have been up to 60 mg/m^3, especially for workers storing jute bags of talc in wagons. Before 1985, the highest levels of exposure to dust for site cleaning staff were estimated to be 30 mg/m^3; for sacking and drying, exposure levels in the workplace before 1975 were estimated to be 20 mg/m^3.

Wild *et al.* (2002) also provided some additional exposure information for three Austrian mines and their respective mills in the Styrian Alps. The ore mined at one site

(site B) consisted of a talc–chlorite mixture with gange [dead rock] inclusions of about 25% (mainly alumino-silicate rock). The gange was dumped in the mine so that the milled product was talc–chlorite and contained between 0.5 and 4% quartz. At site C, the material mined was a talc–dolomite aggregation with a medium talc content of 25%. The amount of quartz in the end-product was below 1%. However, materials from certain parts of this mine that were rich in dolomite could have contained 2–3% quartz. At site D, a light greyish quartz–chlorite–mica schist (alumino-silicate rock that consisted of an aggregation of more or less equal proportions of mica, chlorite and quartz) was mined and milled. Analyses of dust from the lungs and lymph nodes of employees in the Austrian talc industry confirmed the presence of quartz and the absence of amphibole and serpentine (Friedrichs, 1987). Table 1.11 summarizes the levels of exposure reported in the French and Austrian talc mines and associated mills.

Table 1.11. Levels (mg/m^3) of exposure to respirable dust in one French and two Austrian talc mines and associated mills

Exposure group	Occupation	Mine/mill	No. of samples	Mean	Range	Date
No exposure	Office workers	French talc quarry	168	0.2		1986
Low exposure (<5 mg/m^3)	Maintenance workers, garage mechanics, production workers with dust control/LEV	French talc quarry	100	0.5–2.6	0.11–17	1986
		Austrian mine B	173		0.02–4.61	1988–92
		Austrian mine C	33		0.02–4.1	1991–92
Median exposure (5–30 mg/m^3)	Recent production workers	French mine A	193	3.5–25.6	0.21–134	NR
		Austrian mines B and C	17		6.5–19.6	NR
High exposure (>30 mg/m^3)	Milling, maintenance, cleaning	Austria	3		73–159	End of 1980s

From Wild *et al.* (1995, 2002)
LEV, local exhaust ventilation; NR, not reported

Several samples were collected from a crushing, grinding and talcum powder packing unit at a plant in Pakistan to measure different particle sizes (Jehan, 1984). In total, seven 1-hour samples were collected, one for total suspended particles (concentration, 6.14 mg/m^3), one for particulate matter (PM) <10 μm (1.12 mg/m^3), one for PM <7 μm (1.93 mg/m^3), one for PM <5 μm (0.40 mg/m^3), one for PM <3 μm (0.26 mg/m^3), one for

TALC   301

PM <2 μm (0.05 mg/m^3) and one for PM >1 μm (1.55 mg/m^3). Further analyses of the samples with PM <10 μm and <2 μm by scanning electron microscopy showed that the fibre concentration was 0.25 fibres/cm^3 and 0.12 fibres/cm^3, respectively. Analyses by polarized light microscopy indicated the presence of asbestiform tremolite, chrysotile and anthophyllite in these samples.

(b)   User industries

Only limited information is available on exposures in secondary industries in which talc is used or processed further. Results from some surveys are summarized in Table 1.12.

Table 1.12. Mineral composition of talc used for dusting in the rubber industry in the USA

Reference	Location	Date	Mineral composition	Method of analysis
Hogue & Mallette (1949)	Vermont	1943–48	Stated to be 'pure talc'	Impinger
Dement & Shuler (1972)	Canton, MA	1972	2–3% quartz	Gravimetric, optical fibre counts
Fine *et al.* (1976)	Vermont	1972–74	Trace of quartz (<1%), <2 fibres/cm^3	Gravimetric

Personal air samples collected in a rubber band production plant, where housekeeping, ventilation and work practices were poor and talc was used as an anti-sticking agent, had time-weighted average (TWA) concentrations of respirable dust of 2.5–7.8 mg/m^3 (average, 4.8 mg/m^3) for extruders, 5.3 and 6.1 mg/m^3 for vulcanizers and 0.9 and 1.3 mg/m^3 for cutters. Exposures to total dust were found to range from 5.4 to 199 mg/m^3. The talc was reported to contain 2–3% quartz. Within these exposures, 4.7–19.2 fibres were >5 μm/cm^3 as measured by phase-contrast optical microscopy (Dement & Shuler, 1972). [The Working Group noted that no electron microscopic analysis was conducted to confirm the identity of the fibres; however, most of these were probably not asbestos.]

Concentrations of respirable dust in two rubber manufacturing plants where Vermont talc was used as an anti-sticking agent are shown in Table 1.13. Eighteen of 21 samples analysed for quartz contained less than 1% by weight. In 12 samples analysed for fibres, using phase-contrast microscopic techniques for asbestos, all concentrations were less than 2 fibres/cm^3. No electron microscopic fibre analysis was reported (Fine *et al.*, 1976). Hogue and Mallette (1949) found an average dust concentration of 15–50 mppcf [~530–1765 particles/cm^3] talc in two rubber plants that used Vermont talc. Average exposures were 20 mppcf [~706 particles/cm^3] for tube machine operators, 35 mppcf

[1236 particles/cm^3] for tube 'bookers', 15 mppcf [~530 particles/cm^3] for tube cure men
and 50 mppcf [~1765 particles/cm^3] for 'line rerollers'.

**Table 1.13. Concentrations of respirable dust in rubber processing
plants that used talc**

Location	No. of samples	Average dust concentration (mg/m^3)
Plant A		
Lorry and bus inner tubes (splicer)	7	0.60
Lorry and bus inner tubes (cureman)	6	1.41
'Tuber operator'	3	0.47
'Booker'	3	0.74
Farm service inner tubes (splicer)	6	0.82
Farm service inner tubes (cureman)	2	0.91
Plant B		
Rubber band area	6	3.55
Gum engraving room	6	0.64
Hose extruding	4	0.51
Curing heavy duty flaps	3	1.29
'Dust room'	2	0.59

From Fine *et al*. (1976)

In a mortality study of lung cancer and respiratory disease among pottery workers
exposed to silica and talc, Thomas and Stewart (1987) estimated exposure to non-
asbestiform talc and tremolitic talc. Exposure to talc occurred almost exclusively in the
cast shop. Montana steatite talc that had been used to dust moulds since 1955 appeared to
contain no asbestiform talc (Gamble *et al.*, 1982; Grexa & Parmentier, 1979). However,
before 1955, flint and ground clay had been used to dust the moulds. Up to 1976,
tremolitic talc had been used in some glazes. No measurements of airborne talc or silica
were available, and exposure estimates were based on detailed knowledge of industrial
processes and job duties. All exposures to talc were associated with high exposure to
quartz from the clays. Quartz particles from clay are smaller than approximately 4 μm.

Kauppinen *et al.* (1997) developed an international database of exposure
measurements in the pulp, paper and paper product industries. In total, 63 measurements
for talc were included in this database—four measurements in the pulp production and
59 in paper or paperboard production and recycling; 6% of the samples exceeded the
8-hour TWA threshold limit value (TLV) for talc of 2 mg/m^3 respirable dust (ACGIH®
Worldwide, 2005). [No information was provided on the methods of measurement, the
time period when these measurements were taken or the actual processes and the
materials used during these measurements. As only a limited number of measurements
were available, it is improbable that these results are representative of exposure to talc in
this industry.]

Kauppinen *et al.* (2002) described the prevalence of exposure to talc among workers in the on-machine coating of paper. In total, 25 departments were assessed: in 60% of the departments, more than 5% of the workers were exposed to talc, with a median prevalence of exposure of 51–90%. The median level of exposure was assessed as medium (0.6–2 mg/m^3) by a team of occupational hygienists.

Pooley and Rowlands (1975) examined talc imported into the United Kingdom. These talcs were used in a variety of industries, including cosmetics. Only one of the samples examined contained tremolite (>30%). [The number of samples examined and their use were not given. The electron micrograph of the sample identified as tremolite and the concentration of tremolite are consistent with the Gouverneur District New York State talc, which is unlikely to have been used in cosmetics.] All other elongated particles detected in the samples were identified as laths or rolled sheets of talc, chlorite or sepiolite (several samples).

1.3.3   *Consumer exposure*

(a)   Mineralogical characterization

Two studies that were conducted between 1968 and 1977 examined the mineralogy of consumer talc in the USA.

Cralley *et al.* (1968) examined 22 cosmetic talc products that were purchased off the shelf for particles >5 μm with a 3:1 or greater aspect ratio (diameter:length) and found that on average 19% of the particles met these dimensional criteria. [No additional information was provided on the source of the talc products, but the Working Group noted that the authors were located in Cincinnati, OH, USA.] The authors concluded that these 'fibres' were predominantly talc, but suggested that some may have been anthophyllite, tremolite, pyrophyllite or chrysotile. [The Working Group noted that no data were provided to support this statement. The statement was based only on the fact that these minerals have been reported to occur in some talc deposits.] Using X-ray diffraction, quartz was found at a level of 0.2–53.4% in these samples. No limit of detection was given, but the lowest concentration reported was 0.2 wt%. Analysis for other minerals was not carried out.

Rohl *et al.* (1976) examined 20 body powders, baby powders and facial talcums and one pharmaceutical talc, all of which were purchased at retail stores in New York City between 1971 and 1975. Based on X-ray diffraction, optical microscopy and transmission electron microscopy, the concentration of tremolite, anthophyllite and quartz was estimated and the presence of several other minerals was established (see Tables 1.14 and 1.15). One of the 21 samples was composed entirely of cornstarch and one contained primarily pyrophyllite and only a small amount of talc. Quartz was present in nine of the 21 samples, tremolite was reported in nine, anthophyllite in seven and serpentine in two samples. Chrysotile was confirmed by transmission electron microscopy in these samples, but no estimates of the concentrations were provided. Krause (1977), in a review of this study, pointed out that the overlap of the X-ray diffraction patterns of tremolite and

anthophyllite makes accurate estimation of their concentration by this method impossible. A similar problem was pointed out for estimates of the concentration of quartz because of overlap with several talc peaks. [The Working Group believed that these criticisms were reasonable and that little reliance can be placed on the reported concentration of tremolite or anthophyllite. The Working Group also noted that Rohl *et al.* (1976) stated that their methodology did not distinguish between asbestos and non-asbestiform mineral fragments. In addition, the representativeness of these samples for other countries or for other areas of the USA is unclear.]

Table 1.14. Concentrations of minerals in 20 samples of body powders, baby powders and facial talcums and one sample of pharmaceutical talc

Mineral	No. of samples	Concentration range (wt%)
Quartz	9	1.6–35.1
Tremolite[a]	9	0.1–10.3
Anthophyllite[a]	7	2.1–11.4
Chrysotile	2	<0.5[b]

From Rohl *et al.* (1976)
[a] Six samples contained both minerals, which resulted in uncertainty about the absolute concentrations given for each mineral.
[b] Visual estimates by transmission electron microscopy were given as 0.25–0.5%, but no methodology was provided.

Table 1.15. Qualitative measurements of minerals other than anthophyllite, chrysotile, quartz or tremolite in 20 samples of body powders, baby powders and facial talcums and one sample of pharmaceutical talc

Mineral	No. of samples in which the mineral was present
Talc	20[a]
Chlorite	16[b]
Calcite	8[b]
Phlogopite	3[b]
Pyrophillite	2[b]
Dolomite	1[b]
Kaolin	1[b]

From Rohl *et al.* (1976)
[a] Talc was the major mineral in 19 of the 20 samples.
[b] Present in quantities above trace amounts

Paoletti *et al.* (1984) examined talc powders that were used in pharmaceutical and cosmetic preparations. Tremolite was identified in two of six cosmetic talcs on the Italian market. Six of 14 samples provide by the European Pharmacopoeia contained either tremolite, anthophyllite or chrysotile. [No information was provided on the concentration of minerals, including tremolite and quartz, or on the time of purchase.]

Jehan (1984) reported on commercial cosmetic-grade talc (baby and body talcum powder) used in Pakistan between 2000 and 2004. Sixty samples were analysed using atomic absorption techniques, X-ray diffraction, polarized light microscopy and scanning electron microscopy, and the presence of asbestiform chrysotile, both asbestiform and non-asbestiform tremolite and anthophyllite was identified. Asbestiform varieties of tremolite and anthophyllite were uncommon, while chrysotile was common. Respirable quartz was also identified in most (80%) of the samples.

Some products listed by the Cosmetic and Toiletries Formulations Database are shown in Table 1.7. Listing is voluntary and may not be representative of products that are on the market. Tables 1.16 and 1.17 present the average mineral composition of commercial products that were sold under the name of talc in North America and Europe, respectively, in the late 1980s.

(b)   Use of talc for feminine hygiene

The use of body powder for feminine hygiene can be estimated from the prevalence reported for controls in case–control studies that investigated the association between the use of cosmetic talc for feminine hygiene and the risk for ovarian cancer.

The prevalence of ever use in these studies is summarized in Table 1.18. Higher prevalences were generally reported in studies from Canada, the United Kingdom and the USA (up to 59%), whereas the lowest prevalences were generally reported in studies conducted in other countries, including China, Greece and Israel (2.2–5.6%).

Studies with high prevalences also reported doses in terms of frequency, duration of use, age at first use or cumulative doses. Frequency of use may vary from a few times per month to more than once a day, and a large proportion of use is more or less daily. Duration of use ranges up to more than 40 years. The cumulative exposure to talc by perineal dusting was over 10 000 days in 4% of the users in one study (Cook *et al.*, 1997). The use of talcum powder for feminine hygiene is acquired in young adulthood, since 80% of women who use body powder start before the age of 25 years (Harlow & Weiss, 1989).

The types of application also vary. Body powder can be applied perineally, on napkins or on underwear. Dusting of the perineum after bathing appears to be the most frequent single type of application, but simultaneous uses have also been reported. Alternatively, exposure may occur as a result of storing a diaphram in body powder or contamination from the male partner who has used body powder. One study in the USA reported that the use of deodorant spray had a prevalence of 24% (Cook *et al.*, 1997).

In several of the studies in Table 1.18, the interviews on powder use occurred before 1988. Of these, all but one were conducted in the USA. Information on the composition

Table 1.16. Average mineralogical composition (%) of commercial products sold under the name of talc in North America

	Canada			Vermont				California	Texas	Montana		New York
Talc production (thousand tonnes)	40 floated	10	30	70	30 floated	200	12 floated	10	307	326	20	140
Mineral (%)												
Talc	92.5	64.5	60.5	55	90	52.5	94.5	54	80	94	8	25
Chlorite	3	11.5	10.5	7	7	9	1.5	5	1	4.5	85.5	
Dolomite	1	4	8	2	0.5	2	0.5	9	12.5	0.5	0.5	
Magnesite	1.5	17	18	34	2	33.5	0.5	16		T	T	
Serpentine			T									25
Quartz									T	T	T	
Mica	T	T							T	T	T	
Calcite	T											
Tremolite												44
Anthophyllite												5

From Ferret & Moreau (1990)

T, identified mineral that could not be measured by the methods of analysis used

Table 1.17. Average mineralogical composition (%) of commercial products sold under the name of talc in Europe

	Finland		Sweden	Norway	United Kingdom	France	Austria	Italy				Spain		
Talc production (thousand tonnes)	75 floated	250 floated	15	50	17	320	80	20	40	46	17	33	20	28
Mineral (%)														
Talc	93	88	64	55	54	59	51.5	51.5	86	51	47	89	80.5	53
Chlorite	3.5	8.5	16.5	11	9	39	42	43	9.5	19.5	22.5	6	12	18.5
Dolomite	0.5	T	11.5	2	2	1.5	1	2	1.5	12	14.5	2	1.5	6
Magnesite	1.5	2		29	30.5		1		0.5	10	14.5			18.5
Serpentine										T	T			
Quartz			T	T	T	T	T			T			T	
Mica			T			T	T					1.5	1.5	
Calcite			T	T			T			T		0.5	T	
Tremolite			T											

From Ferret & Moreau (1990)

T, identified mineral that could not be measured by the methods of analysis used.

Table 1.18. Assessment of exposure to body powders in the perineal area by women

Location	No. of controls	Prevalence of ever use of talc	Type of perineal use of powder by women	Reference
Massachusetts, USA	215	28.4%	Exposure to talc by dusting	Cramer *et al.* (1982)
Washington DC, USA	171	1.8%	Body talc	Hartge *et al.* (1983)
California, USA	539	45.8%	Use of talcum powder	Whittemore *et al.* (1988)
United Kingdom	451	59.0%	Use of talc	Booth *et al.* (1989)
Washington, USA	158	40.5%	Exposure to powder (cornstarch, baby powder, talc, deodorizing powder); detailed information on type of powder used	Harlow & Weiss (1989)
Massachusetts, USA	239	39.3%	Exposure to baby powder, deodorizing or scented powder	Harlow *et al.* (1992)
China	224	2.2%	Dusting powder	Chen *et al.* (1992)
Maryland, USA	46	17.3%	Genital bath talc (also asked use on napkins or diaphragm)	Rosenblatt *et al.*(1992)
Athens, Greece	193	3.6%	Local application of talc	Tzonou *et al.* (1993)
Israel	408	5.6%	Use of talc	Shushan *et al.* (1996)
Toronto, Canada	564	35.6%	Regular application of talc	Chang & Risch (1997)
Washington, USA	422	39.3%	Dusting with cornstarch, talcum powder, baby or scented powder, and deodorizing spray	Cook *et al.* (1997)
New York, USA	50	26%	Use of talc	Eltabbakh *et al.* (1998)
Montreal, Canada	170	4.7%	Use of talc	Godard *et al.* (1998)
New England, USA	523	18.2%	Use of talc, baby or deodorizing powders or cornstarch	Cramer *et al.* (1999)
New York, USA	693	35%	Use of talc (on genital or thigh area and sanitary napkins)	Wong *et al.* (1999)
Delaware Valley, USA	1367	40%	Use of talc (on genital/rectal area and feet, sanitary napkins, underwear, diaphragm/cervical cap, male partner user)	Ness *et al.* (2000)
California, USA	1122	37.1%	Use of talcum powder	Mills *et al.* (2004)
USA	78 630 cohort	40.4%	Use of talc	Gertig *et al.* (2000)

of baby powder, body powder, facial powder and pharmaceutical talcum powder on the market in New York City before 1976 suggests that many of these products were impure and contained anthophyllite, carbonate, chlorite, chrysotile, phlogopite, pyrophyllite, quartz and tremolite (Cralley *et al.*, 1968; Rohl *et al.*, 1976). After 1976, these powders probably did not contain anthophyllite, chrysotile or tremolite but may have contained up to 10% of other minerals including carbonate, chlorite and quartz (Grexa & Parmentier, 1979). In 1994, baby talcum powder available in the USA typically contained 99% talc; body powder typically contained 65–70% talc and the remaining material was cornstarch, sodium bicarbonate and fragrance (Zazenski *et al.*, 1995).

(c)   Other uses of cosmetic talc

Russell *et al.* (1979) and Aylott *et al.* (1979) reported exposure to respirable dust during the use of talcum powders on the face, body and babies. Russell *et al.* (1979) took 48 measurements during baby dusting operations and 44 measurements during the application of powders to adult bodies. Adult exposure was assessed during normal face/body powdering practices by placing cyclone samplers on shelves at an appropriate height or by positioning a cyclone attached to a headband near the nose (i.e. in the breathing zone). Exposure to respirable dust was 2.03 ± 1.48 mg/m^3 during adult application and was estimated to be 0.19 mg/m^3 for babies. The estimated duration of the application was 1.23 minute for adults and 0.52 minute for babies.

Aylott *et al.* (1979) measured levels of exposure to respirable dust during the application of loose face powder (24 measurements), adult dusting powder (43 measurements) and baby dusting powder (32 measurements). In the study of baby dusting powder, a doll was used. The exposure to respirable dust during face powdering ranged from <0.1 to 1.7 mg/m^3 (duration, 10–25 seconds), that for adult dusting powder ranged from 0.2 to 3.3 mg/m^3 (duration, 15–80 seconds) and that for baby powders ranged from <0.1 to 0.9 mg/m^3 (duration, 15–60 seconds).

(d)   Other exposures

Talc is used as a surface lubricant on the majority of condoms manufactured; contact with condoms may also represent a direct means of exposure of the female genital tract to talc (Kasper & Chandler, 1995).

Exposure to talc can also occur during surgical procedures when using powdered gloves. Talc particles were observed in the navels of small children, in the testes, on the vocal cords, in the urinary bladder tract and after removal of varicous veins (Ramelet, 1991; Simşek *et al.*, 1992). During breast implantations, it is possible that talc from surgical gloves can lead to unwanted encapsulation (Chandler & Kasper, 2003).

1.3.4   *Environmental exposure*

Talc is often detected as a common anthropogenic contaminant in suspended sediment, even in remote snowfields in the Alps; this has been ascribed to its emission

into the atmosphere by industrial and agricultural process (Hillier, 2001). Talc had also been identified in the sediment of the River Don in Scotland (United Kingdom), although no obvious industrial or agricultural sources of the talc were apparent (Hillier, 2001).

1.4   Regulations and guidelines

Occupational exposure regulations and guidelines for talc in several countries are presented in Table 1.19.

Table 1.19. Occupational exposure standards and guidelines for talc

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
Australia	2.5	TWA	
Belgium	10 (I)	TWA	
	2	TWA	
China	3 (T)	TWA	
	4	STEL	
Canada			
Alberta	2 (R)	TWA	
British Columbia	2 (R)	TWA	
Ontario	2 fibres/cm^3 (R)	TWA; value is for particulate matter containing <1% crystalline silica	
Quebec	3 (R)	TWA (talc–containing no mineral or asbestos fibres)	
Czech Republic	10 (R)	TWA; fibres >5%	
	2 (R)	TWA; fibres ≤5%	
	10 (T)	TWA	
Denmark	0.3 fibres/cm^3	TWA; containing fibres	K
Finland	5	TWA	
Germany	(R)	MAK; without asbestos fibres	3B
Hong Kong	2 (R)	TWA	A4
Ireland	10 (I)	TWA	
	0.8 (R)	TWA	
Japan	0.5 (R)	TWA	
	2 (T)	TWA	
Malaysia	2 (R)	TWA	
Mexico	2 (R)	TWA	A4
Netherlands	1 (R)	TWA	
New Zealand	2 (R)	TWA	
Norway	2 (R)	TWA	
	6 (T)	TWA	

TALC   311

Table 1.19 (contd)

Country or region	Concentration (mg/m^3)	Interpretation	Carcinogenicity
Poland	1 (R)	TWA	
	4 (I)	TWA	
South Africa	1 (R)	TWA	
	10 (I)	TWA	
Spain	2 (R)	Ceiling; containing no asbestos fibres and <1% crystalline silica	
Switzerland	2	TWA	
United Kingdom	1 (R)	TWA	
USA			
ACGIH (TLV)	2 (R)	TWA; containing no asbestos	A4
NIOSH (REL)	2 (R)	and <1% crystalline silica	
OSHA (PEL)	~3 (20 mppcf)	TWA (10-h)	
		TWA; containing <1% quartz	

From Direktoratet for Arbejdstilsynet (2002); Työsuojelusäädöksiä (2002); SUVA (2003); ACGIH® Worldwide (2005); Deutsche Forschungsgemeinschaft (2005); Health and Safety Executive (2005)
ACGIH, American Conference of Governmental Industrial Hygienists; I, inhalable dust; MAK, maximum concentration in the workplace; mppcf, millions of particles per cubic foot; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; R, respirable dust; REL, recommended exposure limit; T, total dust; STEL, short-term exposure limit; TWA, 8-h time-weighted average (unless otherwise specified)
[a] 3B, substances for which in-vitro test, or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories; K, included in the list of substances considered as carcinogenic; A4, not classifiable as a human carcinogen

The Food and Drug Administration regulates talc in the USA, and states that it is generally recognized as safe for use in colour additives in foods, drugs and cosmetics, and in paper, paper products, cotton and cotton fabrics that come into contact with food. The Food and Drug Administration also states that talc is present in over-the-counter astringent drug products (National Toxicology Program, 2000).

The Food Chemical Codex (2003) provides specifications for food-grade talc, including the statement that "talc derived from deposits that are known to contain associated asbestos is not food grade." Under the voluntary guidelines initiated in 1976, the Cosmetic, Toiletry, and Fragrances Association stated that all cosmetic talc should contain at least 90% platy talc (hydrated magnesium silicate) that is free from detectable amounts (<0.5%) of fibrous, asbestos minerals (Gilbertson, 1995; Zazenski *et al.*, 1995; National Toxicology Program, 2000).

The current Occupational Safety and Health Administration (2005) permissible exposure level for non-asbestiform talc in the USA is ~3 mg/m^3 (20 mppcf) measured as respirable dust. The current American Conference of Governmental Industrial Hygienists TLV-TWA is 2 mg/m^3 (15 mppcf), which also is the proposed Occupational Safety and Health Administration limit. Levels of exposure of workers may exceed three times the TLV-TWA for no more than 30 minute during the workday (National Toxicology Program, 2000).

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TALC   313

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314   IARC MONOGRAPHS VOLUME 93

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TALC   315

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TALC   317

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2. Studies of Cancer in Humans

2.1   Occupational exposure

2.1.1   *Talc miners and millers* (Table 2.1)

Rubino *et al.* (1976) conducted a study of mortality among men who had begun work
in the mines and mills of a talc operation in the Germanasca and Chisone valleys
(Piedmont), Italy, between 1921 and 1950 and who had been employed for at least 1 year
in a job that involved exposure to talc. A total of 1514 miners and 478 millers were
identified, of whom 168 miners (11.1%) and 40 millers (8.4%) were lost to follow-up
before the end of the study in June 1974, yielding a combined cohort of 1784 men
(89.6%) for analysis. The talc from these mines was described as pure and was reported to
have been used in the pharmaceutical and cosmetics industries. However, due to the
presence of 'footwall contact rocks' and rock-type inclusions in the mines, drilling
operations were associated with exposure to dusts that contained high levels of silica;
such inclusions were removed before milling and talc products were reported to have a
content of free silica below 2%. [The Working Group understood that the term 'silica'
was in fact quartz.] In a few instances, talc samples from the area showed small amounts
of tremolite when examined by X-ray diffraction, but no amphibolic asbestos or
chrysotile were detected. For each worker, cumulative exposure was estimated from
regular measurements of respirable dust content in the air of mines and mills during the
period 1948–74 and individual work histories were abstracted from files of the mining
company. Periods of time during which the dust level was assumed to be uniform were
first selected and cumulative exposure was then calculated as the summed product of the
number of years in each specific working period (years) and the associated dust levels
(million particles per cubic foot; mppcf), resulting in an overall measure of mppcf–years.
Once individual cumulative exposures had been assigned, miners and millers were then
classified separately into low, medium and high levels of exposure. Ranges of exposure
(mppcf–years) for miners were 566–1699, 1700–5665 and 5666–12750, respectively;
ranges of exposure for millers were 25–141, 142–424 and 425–906, respectively. For
each of the 1784 workers included (1346 miners and 438 millers), one unexposed control
subject was chosen at random from among male inhabitants of a nearby small, rural town.
The control was matched to the talc worker on year of birth and vital status at date of
entry into the study [date not specified]. Cause of death for 885 (95.1%) of 931 deceased
workers and 1067 (94.8%) of 1126 deceased controls was obtained from regional death
certificate files supplemented with information from relatives, physicians and medical
records. Observed numbers of deaths among talc workers were compared with expected
numbers, calculated by the use of age-specific mortality rates experienced by the control
cohort. The standardized mortality ratio (SMR) for all causes combined was 0.9 (95%

Table 2.1. Cohort studies of mortality from and incidence of cancer in populations occupationally exposed to non-asbestiform talc

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1976), Germanesca and Chisone valleys (Piedmont), Italy	1992 male talc workers (1514 miners, 478 millers) employed >1 year in talc-exposed job during 1921–1974; hired 1921–1950; mortality follow-up, 1921–74; vital status, 90%; cause of death: 95% of exposed workers, 95% of controls	Occupational history from plant records; respirable dust measurements, 1948–1974; quantitative estimation of cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (million particles per cubic foot, mppcf); classification of workers into 3 levels of exposure	All cancers			**SMR**	Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town; controls matched on vital status at date of entry into study; miners and millers exposed to a very pure form of talc; miners also exposed to inhalable silica; significantly elevated SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma; no smoking data for exposed workers or unexposed controls
				All miners	100	0.8 (0.6–0.9)	
				All millers	42	0.9 (0.7–1.2)	
				Miners (mppcf–years)			
				Level 1: 566–1699	38	1.2 (0.8–1.6)	
				Level 2: 1700–5665	28	1.0 (0.7–1.4)	
				Level 3: 5666–12750	34	0.9 (0.6–1.2)	
				Millers (mppcf–years)			
				Level 1: 25–141	18	1.1 (0.2–3.2)	
				Level 2: 142–424	13	1.3 (0–2.9)	
				Level 3: 425–906	11	0.7 (0.4–2.7)	
			Lung, bronchus and trachea	All miners	9	0.5 (0.2–0.9)	
				All millers	4	0.6 (0.2–1.6)	
				Miners (mppcf–years)			
				Level 1: 566–1699	3	1.1 (0.6–1.7)	
				Level 2: 1700–5665	1	0.5 (0.7–2.3)	
				Level 3: 5666–12750	5	1.1 (0.4–1.3)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	1.7 (0.3–4.9)	
				Level 2: 142–424	1	1.25 (0–7.0)	
				Level 3: 425–906	0	–	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1979), Germanesca and Chisone valleys (Piedmont), Italy	1678 male talc workers (1260 miners, 418 millers); mortality follow-up, 1946–74	Same exposure categories as Rubino *et al.* (1976)	Lung	All miners	8	**SMR** 0.5 (0.2–0.9)	Re-analysis of cohort reported in Rubino *et al.* (1976); SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50
				All millers	4	0.7 (0.2–1.7)	
				Miners (mppcf–years)			
				Level 1: 566–1699	2	0.5 (0–1.9)	
				Level 2: 1700–5665	1	0.2 (0.5–1.2)	
				Level 3: 5666–12750	5	0.6 (0.2–1.4)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	2.0 (0.4–5.8)	
				Level 2: 142–424	1	0.7 (1.7–3.7)	
				Level 3: 425–906	0	–	
Selevan *et al.* (1979), Vermont, USA	392 white male talc workers (163 miners, 225 millers) employed >1 year between 1940 and 1969; mortality follow-up: date of first radiogram, 12-month employment anniversary or January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of death: 94%	Historical insufficient information to calculate cumulative exposure histories; cohort classified into two work areas: mining and milling.	All causes	Total cohort	90	**SMR** 1.2 [0.9–1.4]	Adjusted for age, sex, race, calendar year; US death rates: 1940–67; linear extrapolation for all causes of death: 1967–69. Vermont death rates for specific causes of death: 1949–75; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in mine; radiographic evidence of pneumoconiosis in most workers who died from non-malignant respiratory disease
				Millers	44	1.2 [0.9–1.6]	
				Miners	34	1.3 [0.9–1.8]	
			All cancers	Total cohort	16	[1.3 (0.7–2.0)]	
				Millers	5	[0.8 (0.3–1.9)]	
				Miners	7	[1.7 (0.7–3.5)]	
			Respiratory cancer	Total cohort	6	[1.6 (0.6–3.5)]	
				Millers	2	[1.0 (0.1–3.7)]	
				Miners	5	[4.3 (1.4–10.1)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al.* (1990), northern and western Norway	389 male talc-exposed workers (94 miners, 295 millers) employed >1 year in mine (1944–72) or >2 years in mill (1935–72); mortality and cancer incidence follow-up; 1953–87	Subjective assessment of exposure by experienced colleagues; workers classified by total duration of employment in jobs with low, medium, high and unknown exposure	All causes	*Total cohort* Miners Millers	117 27 90	**SMR** 0.8 (0.6–0.9) [0.8 (0.5–1.2)] [0.7 (0.6–0.9)]	Adjusted for age, smoking (miners only); national death rates: 1953–87; main minerals in mined talc deposit were talc and magnesite; 90% of raw material for mill from mine; 10% from India; no information on smoking habits for millers; smoking habits for miners above national average; low levels of exposure to radon daughters
			All cancers	*Total cohort* Miners Millers	26 9 17	0.8 (0.5–1.1) [1.3 (0.6–2.5)] [0.6 (0.4–1.0)]	
			All cancers	*Total cohort* Miners Millers *Years employed* 1–4 5–19 >20 *Years since first employment* 1–19 20–29 >30	46 15 31 11 19 16 6 18 22	**SIR** 0.9 (0.7–1.2) [1.4 (0.8–2.3)] [0.8 (0.5–1.1)] [1.1 (0.6–2.1)] [0.8 (0.5–1.2)] [0.9 (0.5–1.5)] [0.4 (0.2–0.9)] [1.1 (0.7–1.8)] [1.1 (0.7–1.6)]	

TALC

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al*. (1990) (contd)			Lung	*Total cohort*	6	0.9 (0.3–2.0)	
				Miners	2	[1.6 (0.2–5.7)]	
				Millers	4	[0.8 (0.2–2.0)]	
				Years employed			
				1–4	0	–	
				5–19	3	[1.0 (0.2–3.0)]	
				>20	3	[1.0 (0.2–3.0)]	
				Years since first employment			
				1–19	2	[1.1 (0.1–4.1)]	
				20–29	1	[0.5 (1.3–2.8)]	
				>30	3	[1.1 (0.2–3.2)]	
			Stomach	*Total cohort*	6	1.1 (0.4–2.2)	
				Miners	3	[2.5 (0.5–7.4)]	
				Millers	3	[0.7 (0.1–2.1)]	
				Years employed			
				1–4	2	[2.0 (0.2–7.2)]	
				5–19	2	[0.8 (0.1–2.6)]	
				>20	2	[1.2 (0.1–4.3)]	
				Years since first employment			
				1–19	1	[0.6 (1.4–3.1)]	
				20–29	2	[1.1 (0.1–4.0)]	
				>30	3	[1.7 (0.3–4.8)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000), Luzenac, France	1160 talc workers (1070 men, 90 women) actively employed in 1945 or hired during 1945–94 and employed >1 year; mortality follow-up,,1945–96; vital status: 97%; cause of death: 74% pre-1968 and 98% post-1968	Exposures assessed for case–control study; semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1986 onwards) and subjective assessments by experienced workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.	All causes	*Male talc workers* Pre-1968 (national rates) Post-1968 (national rates) Post-1968 (regional rates)	101 294 294	**SMR** 0.8 (0.6–1.0) 0.8 (0.7–0.9) 0.9 (0.8–1.0)	Adjusted for age, sex, smoking, prior exposure to quartz (case–control study only); partial overlap of study population with Leophonte *et al.* (1983) and Leophonte and Didier (1990); extent of overlap unknown; national mortality rates applied: pre- and post-1968; regional mortality rates applied: post-1968: excess mortality from lung cancer disappeared when national rates applied
			All cancers	Post-1968 (regional rates)	80	1.0 (0.8–1.3)	
			Lung	Post-1968 (regional rates) Post-1968 (national rates)	21 21	1.2 (0.8–1.9) 0.9 (0.6–1.4)	
				Men <60 years of age Latency period <20 years Duration of employment <10 years	7 5 8	2.0 [0.8–4.0] 2.4 [0.8–5.6] 2.1 [0.9–4.1]	
			Stomach	Post-1968 (national rates)	5	1.2 (0.4–2.8)	

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Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000) (contd)	Nested case–control study: lung cancer, non-malignant pulmonary disease and stomach cancer; three randomly selected controls per case; lung cancer: 23 cases, 67 controls	Cumulative exposure estimates (mg/m^3–years) for individual workers.	Lung	Unexposed <100 mg/m^3–years 100–400 mg/m^3–years 400–800 mg/m^3–years >800 mg/m^3–years Per 100 mg/m^3–years	6 5 6 3 3 23	**Odds ratio** 1.0 1.4 2.2 0.7 0.9 1.0 (0.9–1.1)	Unadjusted odds ratio; no increasing trend with increasing cumulative exposure; information on smoking habits available for 52% of cases and 75% of controls Assumes a linear trend
Wild *et al.* (2002), Luzenac, France (1 site), and Styrian Alps, Austria (4 sites)	Austrian cohort: 542 male talc workers employed >1 year during 1972–95; mortality follow-up, 1972–1995; vital status: 97%;. French cohort: as described under Wild (2000)	Austrian cohort: semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1988–92) and descriptions of workplaces from management and long-term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); other exposures coded: quartz, other carcinogens, underground work	All causes All cancers Lung Stomach	French cohort Austrian cohort French cohort Austrian cohort French cohort Austrian cohort French cohort Austrian cohort	294 67 80 17 21 7 5 1	**SMR** 0.9 (0.8–1.0) 0.8 (0.6–1.0) 1.0 (0.8–1.3) 0.7 (0.4–1.2) 1.2 (0.8–1.9) 1.1 (0.4–2.2) 1.2 (0.4–2.8) 0.4 (0–2.3)	Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work (case–control study); study population overlaps with that of Wild (2000); French SMRs calculated by comparison with regional rates, 1968–95; Austrian SMRs calculated by comparison with regional rates, 1972–1995; Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild *et al.* (2002) (contd)	Nested case–control study: lung cancer, non-malignant respiratory disease; three randomly selected controls per case; lung cancer: 23 cases, 67 controls (France); 7 cases, 21 controls (Austria)	Cumulative exposure estimates (mg/m^3–years) assigned to individual workers by occupational physician using work histories abstracted from company records	Lung	Unexposed ≤100 mg/m^3–years 101–400 mg/m^3–years 401–800 mg/m^3–years >801 mg/m^3–years Per 100 mg/m^3–years	9 6 7 5 3 30	**Odds ratio** 1.0 0.9 1.1 0.6 0.7 1.0 (0.9–1.1)	Unadjusted odds ratio; no trend observed with increasing cumulative exposure; trend not affected by adjusting for smoking, quartz exposure, underground work or by lagging the exposure estimate Assumes a linear trend
Coggiola *et al.* (2003), Piedmont, Italy	Cohort of 1974 male talc workers employed >1 year in mine or mill during 1946–95; mortality follow-up, 1946–95; loss to follow-up, 9%; analysis based on 1244 miners, 551 millers	Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years)	All causes All cancers Lung cancer	Total cohort Miners Millers Total cohort Miners Millers Total cohort Miners Millers *Years since first exposure* <20 20–30 >30	880 590 290 185 130 55 44 33 11 6 10 28	**SMR** 1.2 (1.1–1.3) 1.3 (1.2–1.4) 1.1 (1.0–1.2) 1.0 (0.9–1.1) 1.1 (1.0–1.3) 0.9 (0.6–1.1) 0.9 (0.7–1.3) 1.1 (0.7–1.5) 0.7 (0.3–1.2) 1.1 (0.4–2.3) 1.0 (0.5–1.8) 0.9 (0.6–1.3)	Adjusted for age, calendar period; study population overlaps with that of Rubino *et al.* (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946–49; regional rates used for 1970–95, except for cancers of oral cavity, oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Coggiola *et al*. (contd)						**SMR**	
			Oral cavity	Total cohort	31	5.1 (3.5–7.3)	
				Miners	24	6.2 (3.9–9.1)	
				Millers	7	3.3 (1.3–6.9)	
			Oesophagus	Total cohort	10	2.1 (1.1–3.9)	
				Miners	7	2.3 (0.9–4.8)	
				Millers	3	1.8 (0.4–5.2)	
			Stomach	Total cohort	31	1.2 (0.8–1.6)	
				Miners	20	1.2 (0.7–1.8)	
				Millers	11	1.1 (0.5–2.0)	

CI, confidence interval; mppcf, million parts per cubic foot; SIR, standardized incidence ratio; SMR, standardized mortality ratio

confidence interval (CI), 0.8–1.0) for miners and 0.9 (95% CI, 0.8–1.0) for millers. No relationship was observed with increasing time between first exposure and death or with increasing cumulative exposure. Significant increases in specific cause of death among miners were found for silicosis (62 observed; SMR, 2.0; (95% CI, 1.5–2.6) and for silicosis with superimposed tuberculosis (18 observed; SMR, 2.0; 95% CI, 1.2–3.1). These estimates were found to increase with increasing cumulative exposure. A total of 100 deaths from cancers at all sites combined among miners (SMR, 0.8; 95% CI, 0.6–0.9) and 42 deaths among millers (SMR, 0.9; 95% CI, 0.7–1.2) were below those expected. Nine deaths among miners (SMR, 0.5; 95% CI, 0.2–0.9) and four among millers (SMR, 0.6; 95% CI, 0.2–1.6) were due to lung cancer. No excess risk for lung cancer was found in the highest exposure category among miners (cumulative exposure range, 5666–12750 mppcf–years; five observed; SMR, 1.1; 95% CI, 0.4–2.7) or millers (cumulative exposure range, 425–906 mppcf–years; no observed deaths versus 1.3 expected). No cases of mesothelioma were found. [The Working Group noted that the lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study.]

In a re-analysis of their 1976 study, Rubino *et al.* (1979) estimated relative mortality among talc workers using Italian national death rates for men instead of the control cohort. As national rates were available only for the period 1951–74 (end of the study), rates for 1951 were applied for the follow-up period 1946 through to 1950. The number of workers included in this analysis was 1260 miners and 418 millers. In contrast to the previous analysis, the age-standardized mortality for all causes combined was significantly increased for miners (560 observed; SMR, 1.3; 95% CI, 1.2–1.4) as well as for millers (193 observed; SMR, 1.2; 95% CI, 1.0–1.4). Eight observed cases of lung cancer in miners yielded an SMR of 0.5 (95% CI, 0.2–0.9) and four cases in millers yielded an SMR of 0.7 (95% CI, 0.2–1.7). No trend was observed with increasing cumulative exposure for either group of workers [*p*-value for trend not provided]. Mortality from non-malignant respiratory diseases was significantly increased among miners (109 observed; SMR, 3.3; 95% CI, 2.7–4.0), mainly due to 58 cases of pneumoconiosis and 23 cases of tuberculosis. The number of cases of pneumoconiosis and tuberculosis among millers was three and eight, respectively.

Katsnelson and Mokronosova (1979) conducted a study of mortality among male and female workers [numbers not specified] in a talc mining and processing plant in the former USSR in 1949–75. The talc of the area was reported to contain no tremolite or fibrous materials and levels of quartz ranged from 0.2 to 1.6%. Very high mortality ratios were found for cancer at all sites combined (relative risks, 5.1 for men; 6.4 for women; $P < 0.001$) as well as for lung (relative risks, 4.5 for men; $P < 0.02$; 9.3 for women; $P > 0.05$) and stomach cancer (relative risks, 3.7 for men; $P < 0.02$; 6.3 for women; $P < 0.05$) [observed numbers of deaths not specified]. [The Working Group noted that the deaths observed among exposed workers included current and past workers but that the denominator comprised only currently employed persons.]

Selevan *et al.* (1979) used radiography records from the annual surveys of workers in dusty trades of the Vermont Health Department to identify all white male workers employed in the Vermont talc industry for at least 1 year between 1940 and 1969. The study covered three areas that had a total of five companies (two of which ceased operations in 1952 and 1960). The talc in this region is a mixture of pure talc, magnesite, chlorite and dolomite. Airborne dust samples and bulk materials were free of asbestiform minerals, when examined by both X-ray diffraction and analytical electron microscopy. Levels of respirable crystalline silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionally detectable in air samples. Insufficient information was available to estimate cumulative lifetime exposures, but the authors stated that historical data were sufficient to demonstrate past exposure levels for miners and millers far exceeded the standard for non-fibrous talc of 20 mppcf that was in force at the time of the investigation. Due to the more continuous nature of the milling operation, it was considered probable that exposures to dust for millers were higher than those for miners. In one mine that had closed by the time of the study, 'cobblestones' of highly tremolitic serpentine rock were present but were avoided or discarded as far as possible before milling. Miners were also exposed to radon daughters at mean levels ranging up to 0.12 working levels (WL), with single peaks of 1.0 WL. The study groups comprised 163 talc miners and 225 millers. Vital status of workers was ascertained through to 1975, and death certificates were obtained for 85 of 90 deceased cohort members. For non-malignant respiratory disease and respiratory cancer, mortality rates for white men from Vermont were used for comparison, because they were considered to be more appropriate than national rates. For other causes of death, rates for the USA were used. Some increase was noted for all malignant neoplasms combined (16 observed [SMR, 1.3; 95% CI, 0.7–2.0]) and specifically for respiratory cancer (six observed [SMR, 1.6; 95% CI, 0.6–3.5]). [The Working Group noted that the results for respiratory cancer were not analysed by latency.] The excess mortality from respiratory cancer was statistically significant among the miners (five observed [SMR, 4.3; 95% CI, 1.4–10.1]), but not among the millers (two observed [SMR, 1.0; 95% CI, 0.1–3.7]). A significant excess of mortality from non-malignant respiratory disease was seen in millers (seven observed [SMR, 4.1; 95% CI, 1.6–8.4]), but not in miners (two observed [SMR, 1.6; 95% CI, 0.2–5.9]). Most workers who died from non-malignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities).

In two brief communications, Leophonte *et al.* (1983) and Leophonte and Didier (1990) reported on the mortality of workers employed in a talc quarry in Luzenac in the South of France and in the associated talc processing plant. The cohort was composed of those who left employment between 1945 and 1981 and who had worked at the plant for more than 1 year. The talc in this region is a mixture of pure talc, chlorite and dolomite with no asbestos; levels of quartz vary from 0.5 to 3%. Of 470 workers available for study, 256 were alive, 209 had died and five were lost to follow-up. Of 204 workers with a known job history and date of death, 192 had worked exclusively with talc at Luzenac. No significant excess of mortality from cancer in general or specifically from respiratory

TALC   329

and digestive cancers was found. [Observed and expected numbers of cause-specific deaths and associated relative risks were not given.] A significant increase in mortality was found for non-malignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. No cases of mesothelioma were observed. [The Working Group noted the unconventional definition of the cohort and that causes of death were obtained differently for cases (from local doctors, hospitals or families) and controls (from regional or national records).]

Wergeland *et al.* (1990) studied 94 male workers at a talc mine in northern Norway who had been employed in talc-exposed jobs for at least 1 year during 1944–72 and 295 male workers at a talc mill in western Norway who had been employed for at least 2 years during 1935–72. Data on miners were gathered from the company pay rolls, lists of union memberships and the central registry of workers exposed to silica in Norway; data on millers were collected from the company protocol and the local occupational health service. The information included name, date of birth, first and last date of employment and number of periods of employment. According to the authors, Norwegian talc contains only trace quantities of quartz, tremolite and anthophyllite as determined by optical microscopy and by electron microscopic analysis. The talc in the region where the mine was located is composed mainly of pure talc and magnesite. Approximately 90% of the raw material in the mill came from the mine and the rest was imported from India. In addition to talc, dolomite and mica were also processed at the mill. Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3). X-Ray diffractometry indicated that dust samples from both operations contained less than 1% quartz. The mean value for concentrations of radon daughters in the mine was 3.5 pCi/L [0.04 WL], with a range of 1.5–7.5 pCi/L [0.02–0.08 WL]. The majority of the 389 workers could be classified into one of three categories according to degree of dust exposure, based on measurements and qualified assessments of dust level by experienced co-workers. Information on tobacco smoking habits, gathered during the study in 1981, was available for 63 of the 94 miners and showed that smoking rates among these workers were above the national average. Follow-up for cancer incidence (through data linkage to the national cancer registry) and cause-specific mortality (through linkage to the national mortality files) was begun at the date of entry into the cohort or 1 January 1953, whichever came later, and ended at date of death or 31 December 1987, whichever came first. National rates were used to calculate expected numbers of cancers and deaths. The SMR for all causes for the total cohort was 0.8 (117 observed; 95% CI, 0.6–0.9), which reflected a decrease among both miners (27 observed [SMR, 0.8; 95% CI, 0.5–1.2]) and millers (90 observed [SMR, 0.7; 95% CI; 0.6–0.9]). An excess of deaths from all cancers was observed in miners (nine observed [SMR, 1.3; 95% CI, 0.6–2.5]), but not in either the total cohort (26 observed [SMR, 0.8; 95% CI; 0.5–1.1]) or in millers (17 observed; [SMR, 0.6; 95% CI; 0.4–1.0]). Mortality from non-malignant respiratory diseases was decreased, with one observed death among miners [SMR, 0.4; 95% CI, 0–

2.2] and two observed deaths among millers [SMR, 0.2; 95% CI, 0–0.9]. No deaths from pneumoconiosis were reported. The standardized incidence ratio (SIR) for all types of cancer combined was [1.4 (15 observed; 95% CI, 0.8–2.3)] among the miners and [0.8 (31 observed; 95% CI, 0.5–1.1)] among the millers. Two cases of lung cancer were observed among miners [SIR, 1.6; 95% CI, 0.2–5.7] and four cases among millers [SIR, 0.8; 95% CI, 0.2–2.0]. The non-significant excess risk among the miners was confined to cancer of the stomach (three observed [SIR, 2.5; 95% CI, 0.5–7.4]) and cancer of the prostate (four observed [SIR, 2.0; 95% CI, 0.6–5.2]). In the subgroup of 80 workers who belonged to the highest exposure category, a total of six cases of cancer were observed [SIR, 0.4; 95% CI, 0.2–1.0], none of which were cancer of the lung. There were no observed cases of mesothelioma.

Wild (2000) conducted a retrospective cohort mortality study, within a nested case-control study, at the same talc quarry and milling plant at Luzenac as that used by Leophonte *et al.* (1983) and Leophonte and Didier (1990). The cohort included employees who were active in 1945 or hired in the milling plant during the period 1945–94 and who had been employed continuously for at least 1 year. Employees, who were identified from the company files, comprised a total of 1070 men and 90 women. [The authors did not indicate the extent of overlap of the study population with that investigated by Leophonte *et al.* (1983) and Leophonte and Didier (1990).] Dust levels in the 1960s and 1970s were generally high, ranging from below 5 mg/m^3 to more than 30 mg/m^3. Average dust levels dropped to below 5 mg/m^3 in the 1990s through process changes and installation of engineering controls (e.g. installation of a central vacuum system). Overall mortality of the cohort was evaluated from 1 January 1945 to 31 December 1996. Vital status was obtained from the local population register and national mortality files which also included information on cause of death, in most cases, for individuals who died after 1968. Overall, 32 (2.8%) employees were lost to follow-up. Of 106 individuals who died before 1968, cause of death was ascertained for 78 cases. SMRs were calculated using both regional mortality rates (pre- and post-1968) and national mortality rates (pre-1968). When regional mortality rates for 1968 and later were used, the SMR for all causes of death combined was 0.9 (294 observed; 95% CI, 0.8–1.0) for men and 0.8 (11 observed; 95% CI, 0.4–1.4) for women. Eighty men died from cancer at any site (SMR, 1.0; 95% CI, 0.8–1.3) and 21 died from lung cancer specifically (SMR, 1.2; 95% CI, 0.8–1.9). Mortality from lung cancer was non-significantly increased in subgroups of employees who were under 60 years of age (seven observed; SMR, 2.0 [95% CI, 0.8–4.0]), had a latency period of less than 20 years (five observed; SMR, 2.4 [95% CI, 0.8–5.6]) or had a duration of employment of less than 10 years (eight observed; SMR, 2.1 [95% CI, 0.9–4.1]). A slightly increased risk was seen for stomach cancer (five observed; SMR, 1.2; 95% CI, 0.4–2.8). Twenty-six men died from non-malignant respiratory diseases (SMR, 1.1; 95% CI, 0.7–1.6), three of which were pneumoconiosis (SMR, 5.6; 95% CI, 1.1–16.2). When pre-1968 national reference rates were applied, the overall SMR for men was 0.8 (101 observed; 95% CI, 0.6–1.0) and the excess mortality from lung cancer and non-malignant respiratory diseases disappeared. Of

the 101 deaths observed during this period, one was caused by lung cancer (SMR, 0.3 [95% CI, 0.7–1.5]) and five were caused by non-malignant respiratory diseases (SMR, 0.7 [95% CI, 0.2–1.6]). A nested case–control study was performed to investigate further the risks for lung cancer, stomach cancer and non-malignant respiratory diseases in the men of the cohort. For the lung cancer case–control study, 67 controls were individually matched to the 22 cases by age and sex (approximately three controls per case). Information on job history at the plant and tobacco consumption was collected through interviews of subjects who were alive and/or from experienced co-workers. A semiquantitative site-specific job–exposure matrix for talc dust was established using dust levels measured from 1986 onwards and estimates of levels before that year. Information on job history was then converted into estimates of cumulative exposure of the individual employees (expressed as mg/m^3–years). Multiple logistic regression analysis with adjustment for tobacco smoking habits and exposure to quartz estimated the odds ratio for lung cancer to be 0.7 (three cases and 15 controls) and 0.9 (three cases and 10 controls) for employees with a cumulative exposure to talc dust of 400–800 mg/m^3–years and more than 800 mg/m^3–years, respectively, when compared with unexposed employees (six cases and 20 controls). [The Working Group noted that information on smoking habits was available for only 52% of cases and 75% of controls, and that no specific information was given on the proportion of subjects alive among cases and controls at the date of interview.]

Wild *et al.* (2002) conducted a combined analysis of previously published cohort mortality studies among 1070 male employees at a talc quarry and milling plant in the south of France (Site A) (Wild, 2000) and 542 male employees at three talc mines and their respective mills in Austria (Sites B, C and D). The Austrian cohort comprised workers who had been employed for at least 1 year between 1 January 1972 and 31 December 1995. Complete work histories for the Austrian workers were abstracted from company registries and from the regional social insurance. Information on tobacco smoking habits was obtained from earlier unpublished studies of mortality and pneumoconiosis, from colleagues and from records of the compensation claim insurance. Talc from two of the three Austrian plants (Sites B and C) had a content of quartz that was less than 4%, while that of the third plant (Site D) had higher but unspecified levels. Vital status of workers was verified through to 1995, and cause of death for those who had died was obtained from national mortality files. Local mortality rates yielded an overall SMR for the Austrian cohort of 0.8 (67 observed; 95% CI, 0.6–1.0;). A total of 17 deaths were due to cancer at any site (SMR, 0.7; 95% CI, 0.4–1.2), seven of which were from cancer of the lung (SMR, 1.1; 95% CI, 0.4–2.2). One death from stomach cancer (SMR, 0.4; 95% CI, 0–2.3) and no deaths from mesothelioma (0.1 expected) occurred. On the basis of 23 lung cancer deaths observed in the French cohort in 1968–96 and seven in the Austrian cohort in 1972–95, a nested case–control study was conducted. A total of 88 control subjects were selected from the two cohorts, individually matched to cases on age, calendar period and company. All job tasks at the companies were categorized according to measured and estimated levels of talc dust into one of four

exposure groups (no exposure, < 5 mg/m^3, 5–30 mg/m^3 and > 30 mg/m^3). Job histories of cases and controls were converted into cumulative exposure to talc dust by summing the products of duration and level of exposure for each of the tasks held by the subject (mg/m^3–years). Subjects were also categorized according to tobacco smoking habits, exposure to quartz or a history of underground work on a yes/no basis. Information on smoking habits was available for approximately 50% of the cases and 75% of the controls in the French cohort and for 100% of the Austrian cohort. When the no-exposure category was used as the standard (nine cases, 23 controls), the unadjusted odds ratios for lung cancer were as follows: 0.9 (exposure category, 1–100 mg/m^3–years; six cases, 18 controls); 1.1 (exposure category, 101–400 mg/m^3–years; seven cases, 15 controls), 0.6 (exposure category, 401–800 mg/m^3–years; five cases, 21 controls) and 0.7 (exposure category, > 801 mg/m^3–years; three cases, 10 controls). Assuming a linear trend, the odds ratio was 1.0 (95% CI, 0.9–1.1) per unit of 100 mg/m^3–years. Adjustment for tobacco smoking, exposure to quartz or underground work or any two of these variables did not change the results.

Coggiola *et al.* (2003) updated the cohort of Rubino *et al.* (1976, 1979) to include 1974 men who had worked for at least 1 year in the mine and/or in the factory during the period 1946–95. The mortality analysis included 1795 subjects (90.9% of the total cohort; 1244 miners and 551 millers), after excluding 179 workers who were lost to follow-up. No data on smoking habits were available. Follow-up began on 1 January 1946 or the date of first employment and ended at the date of death or 31 December 1995, during which time a total of 880 deaths occurred. The expected number of deaths was calculated from national rates for 1950–69 and regional mortality rates for 1970 onwards (with the exception of cancers of the oral cavity and oesophagus for which regional rates were unavailable; national rates were therefore used). Rates for the early 1950s were applied for the period 1946–49. Total mortality among workers was higher than expected (880 observed; SMR, 1.2; 95% CI, 1.1–1.3), mainly due to excess mortality from non-malignant respiratory tract diseases among the subgroup of miners (105 observed; SMR, 3.1; 95% CI, 2.5–3.7). Of the 105 deaths in this category, 58 were from silicosis. In the combined cohort of workers, there was no excess mortality for all cancers (185 observed; SMR, 1.0; 95% CI, 0.9–1.1) or for lung cancer, in particular (44 observed; SMR, 0.9; 95% CI, 0.7–1.3). No deaths from pleural or peritoneal mesothelioma were found. A significantly elevated risk was seen for cancers of the oral cavity (31 observed; SMR, 5.1; 95% CI, 3.5–7.3) and the oesophagus (10 observed; SMR, 2.1; 95% CI, 1.1–3.9). When the analysis was stratified by job, the SMR for lung cancer was 1.1 (33 observed; 95% CI, 0.7–1.5) among miners and 0.7 (11 observed; 95% CI, 0.3–1.2) among millers. The slight excess found among miners seemed to be due to a slightly elevated risk in workers with less than 20 years since first exposure (latency) (six observed; SMR, 1.1; 95% CI, 0.4–2.3) compared to that of workers with 20–30 years (10 observed; SMR, 1.0; 95% CI, 0.5–1.8) and more than 30 years (28 observed; SMR, 0.9; 95% CI, 0.6–1.3) since first exposure. There was no variation in lung cancer mortality by duration of exposure. Cancer of the oral cavity caused the death of 24 miners (SMR, 6.2; 95% CI, 3.9–9.1) and

seven millers (SMR, 3.3; 95% CI, 1.3–6.9) and oesophageal caused the death of seven
miners (SMR, 2.3; 95% CI, 0.9–4.8) and three millers (SMR, 1.8; 95% CI, 0.4–5.2).
Excess mortality was seen in miners for non-malignant respiratory tract diseases
(105 observed; SMR, 3.1; 95% CI, 2.5–3.7), non-malignant digestive tract diseases
(50 observed; SMR, 1.4; 95% CI, 1.0–1.8) and liver cirrhosis (37 observed; SMR, 1.8;
95% CI, 1.3–2.5). An increased risk for liver cirrhosis was also observed in millers
(18 observed; SMR, 1.7; 95% CI, 1.0–2.7).

Meta-analysis of risk for lung cancer

Wild (2006) performed a meta-analysis of lung cancer mortality among miners and
millers from industries that produced non-asbestiform talc in Vermont, USA (Selevan *et
al.*, 1979), Norway (Wergeland *et al.*, 1990), Italy (Coggiola *et al.*, 2003), France (Wild,
2000) and Austria (Wild *et al.*, 2002). The purpose of the analysis was to compute risk
estimates separately for talc miners, who usually have some co-exposure to silica and/or
radon daughters, and talc millers, who normally have no such co-exposure. Previously
unpublished risk estimates for the subgroup of millers in the French and Austrian cohorts
were used and additional information on smoking habits was obtained for Italian, French
and Austrian workers. Data indicated that the prevalence of smoking was higher than that
in the reference populations [figures not specified]. In the estimation of the overall risk for
millers, data from all five countries were used, while only data from the USA, Norway
and Italy were included in that for miners. Based on SMRs for lung cancer of 1.0 (USA;
two cases; 95% CI, 0.1–3.7), 0.7 (Italy; 11 cases; 95% CI, 0.3–1.2), 1.2 (France; 21 cases;
95% CI, 0.8–1.9), 0.7 (Austria, Site B; three cases; 95% CI, 0.1–2.0) and 1.1 (Austria,
Site C; one case; 95% CI, 0–6.2) and an SIR of 0.8 (Norway; four cases; 95% CI, 0.2–
2.0) for talc millers, a summary SMR of 0.92 (42 cases; 95% CI, 0.7–1.3) was obtained.
No heterogeneity between studies was detected. Similarly, based on mortality ratios for
lung cancer of 4.4 (USA; five cases; 95% CI, 1.4–10.2) and 1.1 (Italy; 33 cases; 95% CI,
0.7–1.5) and an incidence ratio of 1.6 (Norway; two cases; 95% CI, 0.2–5.7) for talc
miners, a summary SMR of 1.2 (40 cases; 95% CI, 0.9–1.6) was found. Due to a
significant heterogeneity of the latter data set, a random effect estimate of the overall
SMR was also calculated (40 cases; SMR, 1.9; 95% CI, 0.7–5.1).

2.1.2   *User industries* (Table 2.2)

Information on risk for cancer among workers exposed to talc is available from
studies that were conducted in user industries. However, they are less informative than
those conducted in talc miners and millers because the potential contamination of talc was
not addressed. In addition, these studies provided no details about the type of talc used.

(a)   *Manufacture of ceramic plumbing fixtures*

Thomas and Stewart (1987) conducted a cohort mortality study of 2055 white men
employed for at least 1 year between 1939 and 1966 at three plants of a single company in

Table 2.2. Cohort studies of mortality from and incidence of cancer in workers occupationally exposed to non-asbestiform talc in user industries

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Manufacture of ceramic plumbing fixtures							
Thomas & Stewart (1987), USA, 5 plants in 1 company	2055 white men employed >1 yearm 1939–66; mortality follow-up through to 1 Jan. 1981; vital status, 96%	Exposure to silica and talc assessed qualitatively by job title–department by industrial hygienist	All causes Lung cancer	Total cohort Total cohort High silica High silica+non-fibrous talc High silica+non-fibrous talc+fibrous talc High silica+no talc	587 52 44 21 5 18	**SMR** 0.9 [0.8–1.0] 1.4 [1.1–1.9] 1.8 [1.3–2.4] 2.5 [1.6–3.9] 1.7 [0.6–4.0] 1.4 [0.8–2.2]	Crystalline silica was the major exposure; also exposure to non-fibrous and fibrous talc
Manufacture of pulp and paper							
Langseth & Andersen (1999), Norway, 10 paper mills	4247 women employed >1 year, 1920–93; follow-up of cancer incidence, 1953–93		All cancers Ovarian cancer Exposure ≥3 years Age 25–35 years Ovarian cancer	Total cohort Paper mill workers	380 37 31 6 18	**SIR** 1.2 (1.1–1.3) 1.5 (1.1–1.2) 1.6 (1.1–2.3) 8.0 (2.9–17.4) 2.1 (1.3–3.4)	Comparison with 5-year age-specific rates in Norwegian women; cancer incidence from National Cancer Registry

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Langseth & Kjaerheim (2004), Norway, 10 paper mills	Nested case–control study in cohort of Langseth & Andersen (1999); 46 cases, 179 matched controls; 100% histologically confirmed	Exposure to asbestos, talc and total dust from work histories, questionnaires by industrial hygienists/ senior employees and international database; personal use of talc: 76% of cases, 57% of controls; personal interviews	Ovarian cancer	Total dust Ever talc Ever asbestos Asbestos according to interview		**Odds ratio** 0.8 (0.4–1.7) 1.1 (0.6–2.2) 2.0 (0.7–5.7) 2.2 (0.5–9.1)	Parity, breastfeeding, tobacco smoking habits, family history of breast or ovarian cancer; conditional logistic regression; odds ratios unchanged after adjustment for confounders
Rubber manufacturing industries							
Blum *et al*. (1979), USA, 2 rubber companies	Nested case–control study; 100 cases, 4 controls per case; matched on age, race, sex, company; 1964–73	Exposure to polycyclic hydrocarbons, nitrosamines, carbon black, talc (high, moderate, low, none) from job histories	Stomach cancer	*Company A* High+moderate talc High talc	27 13	2.4 (1.4–4.1)* 1.3 (0.9–2.5)*	No information on composition or purity of talc; no increase in risk in Company B *90% CI

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Straif *et al.* (1999), Germany, 5 rubber production plants	8933 male blue-collar workers hired after 1 Jan. 1950 and alive 1 Jan. 1981; follow-up, 1 Jan. 1981 to end of 1991; cause of death known for 97% of 1521 deceased	Work histories reconstructed from cost centre codes	Lung cancer Stomach cancer		154 44	**SMR** 1.2 (1.0–1.4) 1.2 (0.8–1.6)	SMRs calculated from national death rates
Straif *et al.* (2000), Germany, 5 rubber production plants	Same as that of Straif *et al.* (1999)	Same as Straif *et al.* (1999) plus semi-quantitative cumulative exposure (low, medium, high) to asbestos, talc, nitrosamines, carbon black for 95% of cohort	Lung cancer Stomach cancer Laryngeal cancer	High talc Medium talc High talc Medium talc High talc Medium talc	21 41 11 12 3 2	1.9 (1.1–3.1) 1.1 (0.8–1.6) 4.3 (2.1–9.0) 1.2 (0.6–2.4) 5.4 (1.1–27.0) 2.8 (0.5–16.7)	Unadjusted; reference: low exposure to talc

CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

TALC   337

the USA that manufactured ceramic plumbing fixtures. Crystalline silica was said to be the major occupational exposure of these workers, but, in some parts of the plant, exposure to fibrous [tremolitic] and non-fibrous [tremolite-free] talc had also occurred. Vital status was ascertained for 96% of the cohort through to 1 January 1981 and observed numbers of deaths were compared with numbers expected from cause-specific mortality rates for white men in the USA. For each job title–department combination, exposure to silica and talc were qualitatively assessed by an experienced industrial hygienist. Silica exposure was categorized as none, low or high; high exposure to silica was further categorized on the basis of no exposure to talc, exposure to fibrous talc and exposure to non-fibrous talc. The SMR for all causes combined was 0.9 (578 observed [95% CI, 0.8–1.0]) and that for lung cancer was 1.4 (52 observed [95% CI, 1.1–1.9]). The excess mortality from lung cancer was seen exclusively among workers who had been exposed to high levels of silica dust (44 observed; SMR, 1.8 [95% CI, 1.3–2.4]) and, to a greater extent, in the subgroup with additional exposure to non-fibrous talc (21 observed; SMR, 2.5 [95% CI, 1.6–3.9]) than in subgroups with additional exposure to fibrous talc (five observed; SMR, 1.7 [95% CI, 0.6–4.0]) or no exposure to talc (18 observed; SMR, 1.4 [95% CI, 0.8–2.2]). [The Working Group noted that all jobs that involved exposure to talc also involved high exposure to respirable silica.]

(b)   *Manufacture of pulp and paper*

Langseth and Andersen (1999) examined cancer incidence among a cohort of 4247 women who had been employed for at least 1 year between 1920 and 1993 in the Norwegian pulp and paper industry. The women had worked mainly in paper sorting and packing departments in 10 paper mills or in administration (85% of the cohort). Production was judged to involve occupational exposures that included paper dusts, microbes, formaldehyde, talc and asbestos (the latter was used as insulation material in boilers and in the breaks of various rolling machines), but no measurement data were available. Women were followed for cancer incidence between 1953 and 1993 and SIRs were calculated by comparing the observed incidence to the 5-year age-specific incidence rates for the female population of Norway. Information on cancer incidence was obtained by linkage with the National Cancer Registry and information on dates of death and emigration was obtained from the Central Bureau of Statistics of Norway. Records of women who died between 1953 and 1960 were identified manually. Between 1953 and 1993, 535 women in the cohort had died, 65 women had emigrated and 380 new cases of cancer had been diagnosed. The SIR for all cancers was 1.2 (380 observed; 95% CI, 1.1–1.3). An excess of ovarian cancer diagnoses was observed (37 observed; SIR, 1.5; 95% CI, 1.1–2.1). In the analyses, workers were also stratified by exposure into the following categories: short-term (< 3 years) versus long-term (≥ 3 years); period of first exposure (1920–39, 1940–59, 1960–74, 1975–93); and time since first exposure (3–14 years, 15–29 years, ≥ 30 years). The excess risk was predominantly seen among women who had been employed in the industry for 3 years or more (31 observed; SIR, 1.6; 95% CI, 1.1–2.3). The excess risk for ovarian cancer was also highest for women under the age of

55 years at diagnosis, with an SIR of 8.0 (six observed; 95% CI, 2.9–17.4) for women aged 25–35 years at diagnosis. Among women who worked in the paper mills, the SIR for ovarian cancer was 2.1 (18 observed; 95% CI, 1.3–3.4). In the discussion, the authors noted that talc is added as a filler in paper mills and may contribute to the excess risk for ovarian cancer observed.

On the basis of an extended follow-up of cohort members for cancer incidence to the end of 1999, Langseth and Kjaerheim (2004) conducted a nested case–control study that included 46 employees who had ovarian cancer and 179 controls individually matched to cases by incidence density sampling. An experienced oncologist reviewed the pathology for all cases. Work histories were obtained from personnel records at each mill. Exposure to asbestos, talc and total dust was assessed on the basis of the work histories, questionnaires on production processes completed by industrial hygienists and senior employees, as well as semiquantitative exposure assessments for the 10 mills extracted from an international database of exposure in the pulp and paper industry. Information on possible confounders (including use of talc on sanitary napkins, underwear or diapers) was obtained for 76% of cases and 57% of controls through a personal interview with the study subject or next of kin. Odds ratios for ovarian cancer were derived by conditional logistic regression. Ever exposure to asbestos was associated with a non-significantly increased odds ratio for ovarian cancer of 2.0 (95% CI, 0.7–5.7), while ever exposure to talc (odds ratio, 1.1; 95% CI, 0.6–2.2) or to total dust (odds ratio, 0.8; 95% CI, 0.4–1.7) was associated with risks that were close to unity. Among women who were interviewed, the odds ratio for exposure to asbestos was 2.2 (95% CI, 0.5–9.1). This estimate was unchanged after adjustment for multiple potential confounders, including parity, breastfeeding, tobacco smoking habits and family history of breast or ovarian cancer. The odds ratios for occupational exposure to talc and total dust were similarly unchanged after adjustment for confounding.

(c)   Rubber manufacturing industries

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum *et al.* (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer in two of the rubber companies from 1 January 1964 to 31 December 1973 (100 deaths in total). Four controls were matched to each case on age, race, sex and company. Using the recorded job history of each worker, the investigators and a group of environmental scientists assessed the potential for exposure (high, moderate, low or none) in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers (anti-sticking agents which were mainly talc). No information was available on the purity or composition of the talc (i.e. whether it contained asbestiform materials or other fibrous or non-fibrous carcinogens). While no clear elevation of odds ratio was reported in Company B, a significantly increased relative risk of 2.4 (27 observed; 90% CI, 1.4–4.1) was found in Company A when workers with moderate and high exposure to talc were

TALC   339

pooled into one group. High exposure in the latter company was associated with a modest increase in relative risk of 1.3 (13 observed; 90% CI, 0.7–2.5).

Based on the employment files of five rubber production plants in Germany, Straif *et al.* (1999) conducted a mortality cohort study of 8933 male blue-collar workers who were hired after 1 January 1950 and who were alive on 1 January 1981. Follow-up was started on the date of completion of 1 year of employment or 1 January 1981, whichever came last, and ended on at death, at 85 years of age, at the date of loss to follow-up or 31 December 1991, whichever came first. Cause of death was obtained for 97% of 1521 deceased workers. Work histories were reconstructed from cost centre codes and were classified into six work areas. SMRs were calculated from national death rates and were estimated at 1.2 (154 observed; 95% CI, 1.0–1.4) for lung cancer and 1.2 (44 observed; 95% CI, 0.8–1.6) for stomach cancer. In a subsequent analysis (Straif *et al.*, 2000), information on work history was combined with semiquantitative levels of exposure to asbestos, talc, nitrosamines and carbon black that were estimated by industrial hygienists to yield overall estimates of cumulative exposure (low, medium, high) for approximately 95% of the cohort. Talc is widely used in rubber production and, according to the authors, asbestos was used in all five plants at least until the early 1980s. In risk analyses that were unadjusted for exposure to asbestos or other potential workplace confounders, high and medium occupational exposure to talc were associated with relative risks for lung cancer of 1.9 (21 observed; 95% CI, 1.1–3.1) and 1.1 (41 observed; 95% CI, 0.8–1.6), respectively, when workers with low exposure were used as the reference group. Equivalent risk estimates were 4.3 (11 observed; 95% CI, 2.1–9.0) and 1.2 (12 observed; 95% CI, 0.6–2.4) for stomach cancer and 5.4 (three observed; 95% CI, 1.1–27.0) and 2.8 (two observed; 95% CI, 0.5–16.7) for laryngeal cancer. Separate risk analyses with adjustment for potential confounders were not performed. [The Working Group noted that risk analyses that adjusted for estimates of exposure to asbestos were not presented.]

2.1.3   *Community-based studies*

Chen *et al.* (1992) conducted a case–control study in Beijing, China, of several risk factors for ovarian cancer that included occupational exposure to talc. A total of 220 cases of newly diagnosed epithelial ovarian cancer were identified between 1984 and 1986 through the Beijing Cancer Registry. Of these, 67 [30.5%] were excluded due to death, 37 [16.8%] due to unavailability of current contact information and four [1.8%] due to patient refusal. The analysis was carried out on 112 cases and 224 community controls, with two age-matched controls per case. Potential controls were excluded if they had a history of serious illness, although the percentage of those excluded for this reason was not specified. In addition, 15 of the 224 eligible controls initially selected [6.7%] refused to participate in the study and were therefore replaced by other eligible controls. No information was provided on the age range of the cases and controls, although the mean age at the time of interview was similar for cases (48.5 years) and controls (49.0 years).

All cases were confirmed by laparotomy and pathological review. Data were collected in-person by trained interviewers. Odds ratios were estimated using conditional logistic regression adjusted for education and parity. Occupational exposure to talc was associated with an odds ratio for ovarian cancer of 0.9 (95% CI, 0.3–2.9). [The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases who were excluded due to death and the exclusion of controls who had a history of serious health problems, which may have resulted in selection bias.]

Hartge and Stewart (1994) analysed the occupational histories of 296 women aged 20–79 years who were diagnosed with ovarian cancer between 1978 and 1981 in the Washington DC area of the USA and 343 hospital-based controls matched to cases on age and race. Pathology was confirmed for all cases. Trained interviewers used a standardized questionnaire to obtain information from each participant on their lifetime job history and occupational exposure to talc. An industrial hygienist blinded to the case status of each participant evaluated each industry and occupation for potential exposure to talc, ionizing radiation, polycyclic aromatic hydrocarbons and solvents, using a scale of 0 (definitely not exposed) to 4 (definitely exposed). Women were considered to be exposed if they had an exposure rating of 2–4 (possibly, probably or definitely exposed). Logistic regression adjusted for race, age, parity, gynaecological surgery and duration of employment in jobs with the exposure of interest was used for the analyses. Controlling for additional known and potential risk factors for ovarian cancer, including parity, oral contraceptive use and cigarette smoking, did not change these estimates. Women who were classified as having been occupationally exposed to talc had odds ratios below the null, although the confidence limits were wide due to the small number of exposed women (12 cases, 31 controls). For women with 10 or more years of employment in an occupation with possible, probable or definite exposure to talc, the odds ratio was 0.5 (five exposed cases; 95% CI, 0.2–1.5). The risk for ovarian cancer was not significantly elevated for any exposure or duration of employment assessed. [Limitations of this analysis include the small number of women occupationally exposed to talc.]

'Industrial talc' was one of the substances evaluated by the exposure assessment team in the community-based case–control study carried out in Montréal, Canada (Siemiatycki, 1991) and described in detail in the monograph on carbon black. About 5% of the 4263 study subjects was considered to be exposed to industrial talc, mostly in the following occupations: painters, motor vehicle mechanics and farmers. Exposure to talc was analysed in relation to 11 different types of cancer, at two levels of exposure (any or substantial). No statistically significant increases in risk were observed. The odds ratios for lung cancer were 0.9 (35 exposed cases; 90% CI, 0.6–1.4) for 'any exposure' and 0.9 (nine exposed cases; 90% CI, 0.5–1.9) for 'substantial exposure'. Prostate cancer was the only site with a borderline significant increased risk, with an odds ratio of 1.4 (29 exposed cases; 90% CI, 1.0–2.1) for 'any exposure' and 1.1 (seven exposed cases; 90% CI, 0.5–2.3) for 'substantial exposure'. [The main limitation of the study was the reliance on expert opinions of exposure rather than measurements for exposure

TALC   341

assessment. Also, exposure levels tend to be lower in such community-based studies than in the workplaces that are selected for cohort studies. The main advantages were the availability of histologically confirmed incident cases and detailed information on tobacco smoking habits and other characteristics of the subjects.]

2.2   Cosmetic use of talc

This evaluation was limited to ovarian cancer because the Working Group was unaware of studies of other cancers associated with the cosmetic use of talc.

The content of body powders used by women varies by product and has changed over time, although data that document this are limited. Before the mid-1970s, body powders may have contained varying but usually small quantities of amphiboles. After that time, amphibole was voluntarily reduced to less than detectable levels, at least in western Europe and the USA. Other non-talc minerals that include chlorite, quartz, carbonates and pyrophyllite may also be found in body powders in varying and occasionally not insignificant quantities in the past and currently. Other added ingredients, which depend on the product, could include cornstarch and perfumes.

2.2.1   *Cohort studies*

Gertig *et al.* (2000) carried out the only prospective cohort analysis that reported an association between perineal use of talcum, baby or deodorant powder and the risk for ovarian cancer. This analysis was conducted among participants in the Nurses' Health Study, a cohort of 121 700 female registered nurses who had been followed since 1976. All participants were between the ages of 30 and 55 years and lived in one of 11 states of the USA at study enrolment. Questionnaires were mailed to participants every 2 years beginning in 1976 to obtain information on the medical history of each woman and potential risk factors for cancer, heart disease and other conditions. The 1982 questionnaire requested information on history and frequency of application of powder to the perineal area (none, daily, one to six times a week, less than once a week) and history of application of powder to sanitary napkins (no/yes). 'Ever talc use' was classified as ever use on either the perineal area or on sanitary napkins. The study population included 78 630 women who responded to the questions on powder use in 1982 and who were not excluded from the analysis for another reason (cancer other than non-melanoma skin cancer before 1982, bilateral oophorectomy, surgery with unknown number of ovaries removed or radiation therapy) and entailed 984 212 person–years of follow-up. Between 1982 and June 1996, 307 incident cases of epithelial ovarian cancer were identified by self-reporting in a biennial questionnaire, by deaths that were reported by relatives or postal authorities or through the National Death Index. Physicians blinded with respect to exposure status reviewed pathology reports to confirm each case and to determine the histological subtype for each tumour as reported by the woman's pathologist. Pooled logistic regression was used to model the incidence rate ratio of ovarian cancer for the

exposed versus unexposed participants. The reported results were adjusted for age in years, parity (defined as the number of pregnancies lasting 6 months or more), duration of oral contraceptive use, body mass index, history of tubal ligation, tobacco smoking status and postmenopausal use of hormones. Additional covariates considered as potential confounders included age at menarche, duration of breastfeeding and age at menopause. Family history of ovarian cancer was not considered to be a confounder, since information on this covariate was not collected until 1992. In 1982, 40.4% of the cohort reported a history of perineal talc use (n = 31 789) and 14.5% reported a history of daily use (n = 11 411). Overall, no association between 'ever use' of talcum powder and total risk for epithelial ovarian cancer (relative risk, 1.1; 95% CI, 0.9–1.4) and no trend of increased risk for ovarian cancer with increasing frequency of talc use were observed. However, a modest increase in risk for serous invasive cancers was associated with any history of talc use (relative risk, 1.4; 95% CI, 1.0–1.9) and a borderline significant trend was found with increasing frequency of use (p for trend = 0.05). Among women without a history of tubal ligation, no association was observed between history of talc use and total risk for epithelial ovarian cancer (relative risk, 1.0; 95% CI, 0.7–1.3). Similarly, history of tubal ligation did not modify the association between the use of talc and risk for serous invasive cancers. [Limitations of this analysis include the availability of exposure information at a single time-point only, the relatively short follow-up period after exposure assessment and the lack of information on age at first use of talc, duration of use of talc, current use of talc in 1982 and use of talc before tubal ligation or pregnancy, all of which are potentially important parameters based on previous studies.]

2.2.2   *Case–control studies* (Table 2.3)

Cramer *et al.* (1982) reported the first epidemiological study of genital talc use and the risk for ovarian cancer. The analysis included 215 cases of epithelial ovarian cancer and 215 population-based controls matched to cases by age (within 2 years), race and residence. All cases were Caucasian, English-speaking residents of Massachusetts, USA, aged 18–80 years, who had been diagnosed with epithelial ovarian cancer between November 1978 and September 1981. Cases were identified through pathology logs or tumour boards of 12 participating Boston hospitals. Among 297 eligible cases identified during the time period of interest, 41 were excluded from the study due to: physician refusal (13), patient refusal (14) or death/change of address (14). An additional 41 cases were excluded because they had a non-ovarian primary (18) or a non-epithelial ovarian tumour based on a review of pathology specimens by the authors. Controls were identified though annual listings of the names, addresses and ages of all Massachusetts residents. Among 475 women identified as potential controls, 11.8% (56) could not be reached, 6.1% (29) were ineligible due to previous bilateral oophorectomy, 4.2% (20) were the wrong age, not Caucasian or did not speak English and 32.6% (155) refused to participate. All cases and controls were interviewed in person to obtain information on their medical history, menstrual and reproductive histories, as well as potential for exposure

Table 2.3. Case–control studies of epithelial ovarian cancer (invasive or borderline) and cosmetic use of talc

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1982) Boston, MA, USA, 1978–81	215 Caucasian, English-speaking women, aged 18–80 years; identified through pathology logs or tumour boards of 12 Boston hospitals; histological confirmation of diagnosis; 215 population-based controls identified through annual listings of names, ages and addresses of all Massachusetts residents; matched by age (±2 years), race, residence	In-person interviews; information collected on medical history, menstrual and reproductive history, potential or definite exposure to talc	'Any' perineal exposure to talc As dusting powder on perineum and sanitary napkins	92 32	1.6 (1.0–2.5) 3.3 (1.7–6.4)	Parity, menopausal status, religion, marital status, educational level, weight, age at menarche, exact parity, oral contraceptive use, postmenopausal use of hormones, tobacco smoking	Distribution of tumour histologies similar for exposed and unexposed cases; potential for talc exposure by way of contraceptives, pelvic surgery or perineal hygiene considered; no information on duration or frequency of talc use; low participation rates among controls (56% of cases matched with no refusals; 27% matched after 1 refusal; 17% matched after 2 or more refusals)
Hartge *et al.* (1983) Washington DC, USA, 1974–77	135 incident cases treated at participating hospitals; 171 population-based controls; frequency-matched by age, race, hospital	Interviews to collect information on reproductive and sexual history, medical history, drug use and other exposures, exposure to talc categorized as 'any' or 'genital' (includes use on genitals, on sanitary napkins or on underwear)	'Any' use of talc 'Genital' exposure to talc	67 7	0.7 (0.4–1.1) 2.5 (0.7–10.0)	Age, race, pregnancy	Questions on talc added after study began; no information on duration or frequency of exposure; no controlling for other potential confounders; potential for selection bias

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Whittemore *et al.* (1988), San Francisco, CA, USA 1983–85	188 incident cases diagnosed at 8 hospitals, aged 18–74 years; histological verification of diagnosis; 539 controls selected from women hospitalized for non-cancerous conditions (*n*=280) or from the population using random digit-dialling (*n*=259); matched by age (±5 years), race, hospital/date of admission (hospital controls) or telephone area code/prefix (population controls)	Structured in-person interviews; information collected on medical history, menstrual and reproductive history, family history, environmental exposures (talc, coffee, alcohol, tobacco); talc exposure categorized by type of application, duration of use prior to tubal ligation or hysterectomy, frequency of use	*Type of application*			Parity, oral contraceptive use	No trend of increasing risk with increasing duration of exposure, as measured in years of talcum powder use on the perineum prior to tubal ligation or hysterectomy; non-statistically significant trend of increasing risk with increasing frequency of exposure, as measured in number of applications of talc to the perineum per month
			Perineum only	22	1.5 (0.8–2.6)		
			Sanitary pads only	5	0.6 (0.2–1.8)		
			Diaphragm only	9	1.5 (0.6–3.6)		
			Any two	67	1.4 (0.9–2.0)		
			All three	1	0.4 (0.0–2.9)		
			Duration of use (years)			Parity	
			None	103	1.0		
			1–9	34	1.6 (1.0–2.6)		
			≥10	50	1.1 (0.7–1.7)		
						Parity	
			Frequency of use				
			Never	97	1.0		
			1–20 times/month	41	1.3 (0.8–2.0)		
			≥20 times/month	44	1.5 (0.9–2.2)		
			30 times/month	–	1.3 (0.9–1.9)		
			p for trend		0.19		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Booth *et al.* (1989), London and Oxford, United Kingdom, 1978–83	235 incident cases from 15 hospitals, aged 65 years or under at diagnosis; diagnosed within 2 years of interview; histological confirmation of diagnosis; 451 hospital-based controls selected from same 15 hospitals; same age distribution as the cases	Interviewer- administered standard questionnaire; information obtained on reproductive and menstrual history, on exposure to exogenous estrogens, cigarettes, talc; talc exposure categorized by frequency of use on perineum and whether it was used to store a diaphragm	*Frequency of use* Never Rarely Monthly Weekly Daily *p* for trend	76 6 7 57 71	1.0 0.9 (0.3–2.4) 0.7 (0.3–1.8) 2.0 (1.3–3.4) 1.3 (0.8–1.9) 0.05	Age, socioeconomic status	Participation rates not provided; questions on talc use added 3 months after start of study; data on talc exposure missing for 18 cases and 17 controls
Harlow & Weiss (1989), western Washington State, USA, 1980–85	116 Caucasian women from 3 urban counties captured in Seattle-Puget Sound Cancer Surveillance System, aged 20–79 years; independent pathological review: 73% of total; histological agreement: 94% of reviewed cases; 158 white population-based controls selected by random-digit dialling; matched by age, county of residence	In-person interviews; information obtained on reproductive, sexual and medical histories, as well as perineal exposure to talc; talc exposure categorized as 'any' perineal use, by method of use, and by type of powder used.	'Any' perineal use *Type of powder used* Cornstarch only Baby powder only Baby powder, combined Talc, unspecified Deodorizing powder only Deodorizing, combined	49 4 18 22 13 10 14	1.1 (0.7–2.1) 0.8 (0.2–3.8) 0.8 (0.4–1.9) 0.9 (0.5–2.0) 1.0 (0.4–2.4) 3.5 (1.2–28.7) 2.8 (1.1–11.7)	Age, parity, use of oral contraceptives	Cases diagnosed with borderline (serous or mucinous) tumours; study limited by incomplete information on powder use and small size; no significant association between method of powder use and risk for borderline tumours

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chen *et al.* (1992), Beijing, China, 1984–86	112 women from Beijing Cancer Registry, with a mean age of 48.5 years; confirmation of diagnosis by laparotomy and pathological examination in all cases; 224 population-based controls selected first on basis of area of residence of cases and then randomly from census lists of all women within 1 year of age of identified case; matched by age; mean age, 49.0 years	Interviewer-administered questionnaire; information obtained on menstrual, obstetric, marital, medical, family and dietary histories as well as exposure to talc (perineally and occupationally); perineal exposure reported as yes/no	Use on perineum or lower abdomen	7	3.9 (0.9–10.6)	Education, parity	Age range of cases and controls not reported

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Harlow *et al.* (1992), Boston, MA, Massachusetts, USA, 1984–87	235 white women from 10 hospitals in metropolitan Boston area, aged 18–76 years; independent pathological confirmation of diagnosis; 239 population-based controls randomly selected from town registers; matched by age (±2 years), race, precinct of residence; no history of bilateral oopherectomy	In-person interviews; information collected on occupational history, medical and reproductive history, dietary history, tobacco smoking, hygienic practices including perineal exposure to talc; exposure to talc categorized by type of application, brand of powders, duration and frequency of use	'Any' perineal use of talc	114	1.5 (1.0–2.1)	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Odds ratio for women with >10 000 lifetime applications unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0); significant increase in odds ratio for women with >10 000 lifetime applications observed after excluding use of talc during non-ovulatory periods and after surgical sterilization (odds ratio, 2.8; 95% CI, 1.4–5.4)
			Method of application				
			Sanitary napkins or underwear only	9	1.1 (0.4–2.8)		
			Partner or applications to diaphragm	20	1.2 (0.6–2.4)		
			Dusting on perineum	85	1.7 (1.1–2.7)		
			Frequency (no. per month)				
			None	121	1.0		
			<5	32	1.5 (0.8–2.7)		
			5–29	24	1.2 (0.6–2.2)		
			≥30	58	1.8 (1.1–3.0)		
			p for trend		0.046		
			Years of use				
			None	121	1.0		
			<10	14	1.2 (0.5–2.6)		
			10–29	49	1.6 (1.0–2.7)		
			≥30	51	1.6 (1.0–2.7)		
			p for trend		0.07		
			Total applications				
			None	121	1.0		
			<1000	18	1.3 (0.7–2.7)		
			1000–10 000	54	1.5 (0.9–2.4)		
			>10 000	42	1.8 (1.0–3.0)		
			p for trend		0.09		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Rosenblatt *et al.* (1992), Baltimore, MD, USA, 1981–85	77 women admitted to Johns Hopkins Hospital as in-patients for treatment or diagnosis; diagnosed within 6 months of admission; residents of the USA; pathological confirmation of diagnosis; 46 hospital-based controls selected from female in-patients with no gynaecological or malignant conditions; matched *a posteriori* by age (±5 years), race, closest date of diagnostic admission	Questionnaire administered by telephone and in the hospital; information collected on genital and respiratory exposure to fibre-containing substances, such as talc; sources of genital exposure included contraceptive methods (diaphragm, condoms), dusting of perineum and sanitary products; sources of respiratory exposure included: use of face and/or body powders; residential or occupational exposure to fibre-containing substances, such as talc, asbestos, fiberglass; estimation of 'dose' by adding number of years of exposure from all sources	Genital fibre use *Method of application* Diaphragm use with powder Genital bath talc Sanitary napkin with talc exposure	67

14

22
21 | 1.0 (0.2–4.0)

3.0 (0.8–10.8)

1.7 (0.7–3.9)
4.8 (1.3–17.8) | Parity

Parity, education No adjustment Highest weight, 1 year prior to diagnosis | Investigators encountered difficulty finding controls who met all of the matching criteria. For analysis, 46 matched sets, of which 31 sets had 2 cases and 1 control; limitations include small study size, broad definition of fibre exposure, limited information available on perineal exposure to talc |

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Tzonou *et al.* (1993), Athens, Greece, 1989–91	189 women hospitalized for ovarian cancer surgery in 2 major cancer hospitals in Greater Athens, aged 75 years or under; histological confirmation of diagnosis; 200 hospital visitor controls (selected from visitors to patients hospitalized in the same wards as cases); not matched to cases by age	Questionnaire administered in hospital by medical residents; information collected on medical and reproductive histories, as well as personal, demographic and socioeconomic variables; qualitative assessment of talc exposure (yes/no use in the perineal region)	*Talc application in perineum* No Yes	 183 6	 1.0 1.1 (0.3–4.0)	Age, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking status, alcohol use, coffee consumption, use of analgesics, use of tranquilizers or hypnotics, use of hair dyes	Study limited by very low prevalence of perineal talc use

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Purdie *et al.* (1995), Queensland, New South Wales, Victoria, Australia, 1990–93	824 incident cases diagnosed and registered in all major gynaecological-oncology treatment centres in 3 states, aged 18–79 years; independent pathological confirmation of diagnosis; 860 population-based controls selected randomly from electoral rolls, stratified by age and geographical region	Interviewer-administered standardized questionnaire in clinic (cases) or home (some cases, all controls); information collected on medical, reproductive, family and occupational histories, as well as dietary factors and history of talc use	Use of talc around the abdomen or perineum	[467] 56.7%	1.3 (1.0–1.5)	Parity; other potential confounders, e.g. contraceptive use, also considered	
Shushan *et al.* (1996), Israel, 1990–93	200 incident cases (164 invasive, 36 borderline) diagnosed and reported to Israel Cancer Registry, aged 36–64 years; histological confirmation of diagnosis; 408 population-based controls selected by random-digit dialing; matched by geographical area	Interviewer-administered standard questionnaire; information collected on reproductive history, use of oral contraceptives and fertility drugs, exposure to talc; exposure to talc stratified into 'never/seldom', 'moderate/a lot'	*Use of talc* Moderate/a lot	21	[1.97] ($p = 0.04$)	No control for confounding	Study limited by the very sparse information on talc use and the unavailability of adjusted results for the association between use of talc and the risk for ovarian cancer

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chang & Risch (1997), metropolitan Toronto and southern Ontario, Canada, 1989–92	450 incident cases (primary, invasive and borderline); aged 35–79 years; histological confirmation of diagnosis; 564 population-based controls identified through provincial records of all homeowners, tenants and family members; randomly selected from same residential area; matched by age within 15-year age groups	Interviewer-administered questionnaire; information collected on menstrual and reproductive history, use of hormones and oral contraceptives, and use of talc; exposure to talc categorized on basis of 'any' exposure, type of exposure, frequency and duration of perineal application	'Any' exposure to talc *Type of exposure* Sanitary napkins After bathing *Frequency of after-bath use (times/month)* None <10 10–25 >25 Per 10 applications per month *Duration of after-bath use (years)* None <30 30–40 >40 Per 10 years of use	198 51 172 76 54 41 60 71 41	1.4 (1.1–1.9) 1.3 (0.9–2.0) 1.3 (1.0–1.7) 1.0 1.8 (1.2–2.7) 1.1 (0.7–1.7) 1.0 (0.6–1.5) 0.9 (0.7–1.1) 1.0 1.7 (1.1–2.6) 1.4 (1.0–2.2) 0.9 (0.5–1.4) 1.1 (1.0–1.2)	Age at interview, duration of oral contraceptive use, parity (number of full-term pregnancies), duration of lactation per pregnancy, history of tubal ligation or hysterectomy, family history of breast or ovarian cancer	Authors do not specify whether cases were identified through a cancer registry or some other reporting mechanism. Borderline significant trend observed with increasing duration of exposure to talc, but not with increasing frequency of exposure

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cook *et al.* (1997) Western Washington State, USA, 1986–1988	313 incident cases (234 invasive, 79 borderline) identified from records of Cancer Surveillance System of western Washington; white residents of three counties (King, Pierce, Snohomish), aged 20–79 years; no information on whether diagnosis was histologically confirmed; 422 white population-based controls selected by random digit-dialling (part of a larger control pool for several studies of cancer in women); matched by age	Structured in-person interviews; information collected on medical and reproductive histories, smoking habits, birth control methods and use of genital powders and deodorant sprays; exposure to genital powders assessed on the basis of 'any' lifetime exposure, method of use and cumulative lifetime exposure (days, months or lifetime applications)	*Lifetime perineal application*			Adjusted for age	
			None	154	1.0		
			Any	159	1.5 (1.1–2.0)	Adjusted for age	
			Exclusive use of powder for				
			Perineal dusting	55	1.8 (1.2–2.9)		
			Diaphragm storage	22	0.8 (0.4–1.4)		
			Dusting sanitary napkins	12	1.5 (0.6–3.6)		
			Deodorant spray	18	1.5 (0.8–3.0)	Adjusted for age and other methods of genital powder application	
			Any use of powder for				
			Perineal dusting	95	1.6 (1.1–2.3)		
			Diaphragm storage	46	1.0 (0.6–1.6)		
			Dusting sanitary napkins	38	0.9 (0.5–1.5)		
			Deodorant spray	40	1.9 (1.1–3.1)	Adjusted for age and other methods of genital powder application	
			Cumulative lifetime perineal dusting (days)				
			None	154	1.0		
			≤2000	20	1.8 (0.9–3.5)		
			2001–5000	24	1.6 (0.9–2.9)		
			5001–10 000	21	1.2 (0.6–2.4)		
			>10 000	28	1.8 (0.9–3.4)		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Eltabbakh *et al.* (1998), Buffalo, NY, USA, 1982–96	'Study' group: 50 women admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute; histological confirmation of diagnosis; 'control' group: 466 women treated for primary ovarian cancer at same centre; pathological review of diagnosis	Self-administered, 44-item questionnaire completed at hospital admission	Perineal use of talc	224 (48.1%)	*p*=0.003	No control for confounding	'Cases for this study were women diagnosed with primary peritoneal cancers. Case definition excluded patients with diagnoses of peritoneal mesothelioma, borderline tumours of peritoneum or invasive ovarian cancer; no healthy controls enrolled in this study. 'Controls' were women diagnosed with primary epithelial ovarian cancer. Control definition excluded patients with diagnoses of non-epithelial ovarian cancer and ovarian cancer secondary to metastases from other sites.

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Godard *et al.* (1998), Montreal, Quebec, Canada, 1995–96	170 incident cases with primary invasive or borderline epithelial tumours, identified at two gynaecological clinics, aged 20–84 years; histological confirmation of diagnosis; 170 population-based controls selected by a modified random-digit dialling method; frequency-matched by age (±1 year), French Canadian ethnicity	Standardized 57-item questionnaire; telephone or in-person interviews conducted with cases, no information on how controls were interviewed; qualitative assessment of perineal talc exposure (ever/never)	'Ever' use of talc on perineum	[18] (10.6%)	2.5 (0.9–6.6)	Age at menarche, age at menopause, parity, age at first and last childbirth, duration of oral contraceptive use, age at last oral contraceptive use, tubal ligation, alcohol use, previous breast or abdominal surgery	

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1999), eastern Massachusetts and New Hampshire, USA, 1992–97	563 incident cases (including borderline tumours) identified through hospital tumour boards or statewide cancer registries; age range not provided; histological confirmation of diagnosis for all cases; 523 population-based controls selected by random-digit dialling and through annual listings of names, ages and addresses of all Massachusetts residents (women over the age of 60 years); frequency-matched by age (±4 years), location of residence	In-person interviews using standardized questionnaire; information collected on medical and reproductive histories, family history and personal habits; multiple questions on potential routes of talc exposure (non-genital, genital, husband's use), brands used, age at first use, duration and frequency of use	No genital exposure	411	1.0	Age, study site, parity, oral contraceptive use, body mass index, family history of breast or ovarian cancer, history of tubal ligation	
			Any genital exposure	152	1.6 (1.2–2.1)		
			Method of use				
			No use	312	1.0		
			Non-genital areas	99	1.1 (0.8–1.5)		
			Dusting perineum	71	1.5 (1.0–2.2)		
			Dusting sanitary napkins	20	1.5 (0.7–3.1)		
			Dusting underwear	8	1.2 (0.4–3.6)		
			More than one method	53	2.2 (1.3–3.6)		
			Frequency (uses/month)				
			None	312	1.0		
			<30	64	2.2 (1.4–3.6)		
			30–39	59	1.7 (0.8–1.8)		
			≥40	23	1.7 (0.8–3.1)		
			Duration of use (years)				
			None	312	1.0		
			<20	55	1.9 (1.2–3.0)		
			20–30	32	1.3 (0.8–2.3)		
			>30	59	1.4 (0.9–2.3)		

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1999) (contd)			*Total no. of applications*				
			None	312	1.0		
			<3000	51	1.8 (1.1–3.0)		
			3000–10 000	36	1.4 (0.8–2.4)		
			>10 000	59	1.4 (0.9–2.2)		
			p for trend		0.16		
			Total no. of applications (censored analysis)				Censored analysis excludes talc applications that occurred during non-ovulatory years or after hysterectomy or tubal ligation. Includes non-genitally exposed women.
			None	312	1.0		
			<3000	59	1.5 (1.0–2.4)		
			3000–10 000	51	1.7 (1.1–2.8)		
			>10 000	36	1.8 (1.0–3.2)		
			p for trend		0.02		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Wong *et al.* (1999) Buffalo, NY, USA, 1982–92	462 incident cases admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute, mean age, 54.9 years; histological confirmation of diagnosis; 693 hospital-based controls treated for non-gynaecological malignancies at same cancer centre; mean age, 54.9 years; frequency-matched to cases by age at diagnosis (±5 years)	Self-administered, 44-item questionnaire completed at hospital admission; information collected on medical, social, family, dietary and occupational histories; method of talc use (never, sanitary napkin, genital/thigh area, both) assessed and duration of use	*Method of use* Never Sanitary napkin Genital or thigh area Both *Duration of use (years)* None 1–9 10–19 ≥20	241 13 157 51 241 39 49 101	1.0 0.9 (0.4–2.0) 1.0 (0.8–1.3) 1.1 (0.7–1.7) 1.0 0.9 (0.6–1.5) 1.4 (0.9–2.2) 0.9 (0.6–1.2)	Age, parity, oral contraceptive use, smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location, history of tubal ligation or hysterectomy	Case population largely that reported by Eltabbakh *et al.* (1998); 32 cases, 39 controls did not recall duration of use.

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Ness *et al.* (2000), eastern Pennsylvania, southern New Jersey, Delaware, USA, 1994–1998	767 incident cases identified at 39 hospitals in the Delaware Valley region; aged 20–69; diagnosis within 6 months prior to interview; pathological review of a random subset of cases (*n* = 120) 1367 population-based controls identified through random digit dialing (≤65 years of age) and Health Care Financing Administration lists (65–69 years of age); frequency matched by age and location of residence	Standardized in-person interviews; information collected on sexual activity, use of contraceptives, menstrual and reproductive history, and history and duration of talc use (genital, non-genital applications, exposure via male sexual partners)	*Method of use* Never Feet, arms, breasts Genital/rectal Sanitary napkin Underwear Diaphragm/ cervical cap Male partner *Duration of use (years)* Never <1 1–4 5–9 ≥10	349 335 161 77 70 10 56 401 17 76 40 233	1.0 1.4 (1.1–1.6) 1.5 (1.2–2.0) 1.6 (1.1–2.3) 1.7 (1.2–2.4) 0.6 (0.3–1.2) 1.0 (0.7–1.4) 1.0 2.0 (1.0–4.0) 1.6 (1.1–2.3) 1.2 (0.8–1.9) 1.2 (1.0–1.5)	Age, parity, race, family history of ovarian cancers, oral contraceptive use, tubal ligation, hysterectomy, lactation	Risk for ovarian cancer compared with 50 women with primary peritoneal cancers; no control for confounding; analysis of duration examined risk for cases reporting use of talc on the feet, genital and rectal areas.

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Langseth & Kjaerheim (2004), Norway, 1953–99	35 (invasive and borderline tumours) selected from cohort of 4247 female pulp and paper workers; cohort follow-up, 1953–99; histological review and confirmation of diagnosis; 121 selected from the cohort by incidence density sampling; matched by birth (year ±2 years); controls had no ovarian cancer and had intact ovaries	In-person interviews conducted at mills or by telephone; information collected on occupational history, household exposure to asbestos, menstrual and reproductive history, hereditary risk of cancer, as well as talc use on sanitary napkins, underwear or diapers or by husband in genital area.	'Ever' use of talc for personal hygiene	12	1.2 (0.4–3.2)	Adjusted for possible confounders, but not explicitly stated	Nested case–control study conducted in a cohort study of 10 pulp and paper mills; many missing values among proxy respondents

TALC

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Mills *et al.* (2004), central California, USA, 2000–01	249 incident cases from 22 counties diagnosed in two regional cancer registries, using rapid case ascertainment procedures; histological confirmation of diagnosis for a subset of cases; 1105 population-based controls identified by random-digit dialling; frequency-matched by age, race, ethnicity	Telephone interview to obtain information on medical history, menstrual and reproductive history, family history of cancer, history of perineal talc exposure (frequency, duration and calendar years of use); 'cumulative' use calculated by multiplying frequency (categorical variable) by duration in months	*Perineal use of talc*			Age, race/ethnicity, duration of oral contraceptive use, breastfeeding. Additional covariates considered to be potential confounders included family history of breast or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation, duration of post-menopausal use of hormones.	Cumulative use calculated as frequency (categorical weighting from 0–3) multiplied by duration.
			Never	143	1.0		
			Ever	106	1.4 (1.0–1.9)		
			Frequency of use				
			Never	143	1.0		
			<1/week	34	1.3 (0.9–2.1)		
			1–3/week	31	1.6 (0.7–1.8)		
			4–7/week	41	1.7 (1.1–2.6)		
			p for trend		0.015		
			Duration of use (years)				
			Never	143	1.0		
			≤3	18	1.0 (0.6–1.8)		
			4–12	32	1.9 (1.2–3.0)		
			13–30	29	1.5 (0.9–2.3)		
			>30	21	1.2 (0.7–2.1)		
			p for trend		0.045		
			Cumulative use				
			Never	143	1.0		
			1st quartile (lowest)	18	1.0 (0.6–1.8)		
			2nd quartile	28	1.8 (1.1–3.0)		
			3rd quartile	34	1.7 (1.1–2.7)		
			4th quartile (highest)	20	1.1 (0.6–1.8)		
			p for trend		0.051		

CI, confidence interval

to talc by way of contraceptives, perineal hygiene or surgery. Ninety-two cases (42.8%) and 61 controls (28.4%) reported a history of regular use of talc as a dusting powder to the perineum, on sanitary napkins or on both. After adjustment for parity (yes/no) and menopausal status (pre-/post-), a significant association was found between 'any perineal use' of talcum powder and the risk for ovarian cancer (odds ratio, 1.9; 95% CI, 1.3–2.9). This association was attenuated but still significant after adjustment for additional potential confounders, including religion, marital status, level of education, weight, age at menarche, parity (number of children), oral contraceptive use, menopausal use of hormones and tobacco smoking (adjusted odds ratio, 1.6; 95% CI, 1.0–2.5). A single type of perineal exposure to talc (either as a dusting powder to the perineum or on sanitary napkins) was associated with a borderline significantly increased risk for ovarian cancer (odds ratio, 1.6; 95% CI, 1.0–2.5) after adjustment for parity and menopausal status, while a history of both types of perineal exposure was associated with a significant increase in risk (adjusted odds ratio, 3.3; 95% CI, 1.7–6.4). No association was seen between other potential sources of exposure to talc (pelvic surgery, use of condoms, use of diaphragm or using talc for diaphragm storage) and the risk for ovarian cancer. In addition, the results were essentially unchanged after excluding women who had had a tubal ligation or hysterectomy (odds ratio, 2.8; $P < 0.003$), although the authors noted that these surgical procedures are usually performed at mid-life when substantial exposure to talc may already have occurred. The distribution of tumour histologies was similar for exposed and unexposed cases; 53.7% of tumours were classified as serous among the unexposed cases and 48.9% among the exposed cases with 'any' perineal use of talc. [Limitations of this report include the lack of information on duration and frequency of talc use. In addition, participation rates among the controls were quite low (50%), although the authors noted in a secondary analysis that, when cases were matched to the first control selected (i.e. 100% participation), a positive association was also found (odds ratio, 2.44; $P < 0.05$).]

Hartge *et al.* (1983) published a brief report of a study conducted between 1974 and 1977 in the Washington DC (USA) area. The study included 197 cases treated for pathologically confirmed epithelial ovarian cancer at participating hospitals and 197 controls treated at the same hospitals for conditions other than pregnancy, malignancies and gynaecological or psychiatric diseases. Controls were frequency-matched to cases by age, race and hospital. Interviews were conducted in the hospital for controls and at home for most cases to collect information on reproductive and sexual history, medical history, drug use and other exposures. Questions on exposure to talc were added after the study began. As a result, the analysis included only 135 cases and 171 controls with information on exposure to talc. Sixty-seven cases [49.6%] and 100 controls [58.5%] reported 'any' use of talc (including non-genital uses), while seven cases [5.2%] and three controls [1.8%] reported genital use of talc (including use on genitals, on sanitary napkins or on underwear). No association was observed between 'any' use of talc and the risk for ovarian cancer (odds ratio, 0.7; 95% CI, 0.4–1.1). This estimate was unchanged after adjustment for race, age and pregnancy. A non-significant positive association was found between genital use of talc and the risk for ovarian cancer (odds

ratio, 2.5; 95% CI, 0.7–10.0). [Limitations of this study included its small size and the low prevalence of genital use of talc, the lack of information on its duration and frequency and age at first use, the lack of control for other potential confounders and the increased potential for selection bias due to different interviewing protocols for cases and controls. In addition, no information was given in this brief report on the methods used in the analysis to control for confounding.]

Whittemore *et al.* (1988) analysed the association between perineal use of talc and the risk for invasive epithelial ovarian cancer among 188 cases and 539 controls in the San Francisco Bay area (CA, USA). Cases were residents of northern California, aged 18–74 years, who had been diagnosed with an invasive ovarian tumour between January 1983 and December 1985 at one of eight hospitals. Controls were either selected from among women who had been hospitalized for a non-cancerous condition at one of these eight hospitals or were identified from the population using random-digit dialling. Women in each control group were matched to each case by age (within 5 years) and race (white, black, other), plus hospital and date of admission (within 3 months) for the hospital controls ($n = 280$) and telephone area code and prefix for the population-based controls ($n = 259$). Structured interviews were conducted in the homes of participants to obtain information on the history, frequency and duration of perineal use of talc, medical history and additional covariates of interest (menstrual and reproductive histories, family history and environmental exposures, such as consumption of alcohol, coffee and tobacco). Of 317 eligible cases, eight (2.5%) were excluded due to physician refusal, 30 (9.5%) due to patient refusal, 44 (13.9%) due to death or incapacitating illness and 47 (14.8%) due to non-invasive tumours, which left 188 (59.3%) for inclusion in the analysis. Among the controls, 68% of the women identified as eligible hospital controls ($n = 354$) and 71% of the women identified by telephone as eligible population-based controls ($n = 329$) agreed to participate. After excluding controls matched to cases with bordeline tumours, 280 hospital controls and 259 population controls were included in the analysis (Wu *et al.*, 1988). Exposure to talc was categorized by type of application (perineum only, sanitary pads only, diaphragm only, any two types of application or all three types of application), duration of use before tubal ligation (none, 1–9 years, ≥ 10 years, unknown) and frequency of use (none, 1–20 applications per month, > 20 applications per month, unknown). Conditional logistic regression was used to calculate the odds ratio for each exposure and to test for trend. Ninety-seven cases (51.6%) and 247 controls (45.8%) reported previous use of talcum powder on the perineum to yield an odds ratio of 1.40 ($P = 0.06$) after adjustment for parity. Since the odds ratios were similar when hospital-based and population-based controls were analysed separately, analyses using the combined group of controls were reported. After adjustment for parity and oral contraceptive use, the odds ratio for use of talc on the perineum only was 1.5 (95% CI, 0.8–2.6). No significant associations were observed with either individual or multiple types of perineal talc use, including the combination of use on the perineum, sanitary napkins and a diaphragm (odds ratio, 1.4; 95% CI, 0.9–2.0 for any two types of use versus 0.4; 95% CI, 0.0–2.9 for all three types combined). No

significant trend was observed with duration of talc use on the perineum before tubal
ligation or hysterectomy. Odds ratios were 1.6 (95% CI, 1.0–2.6) for 1–9 years of
exposure and 1.1 (95% CI, 0.7–1.7) for more than 10 years of exposure. A non-significant
trend of increased risk with increasing frequency of perineal use of talc was observed,
with an overall odds ratio of 1.3 (95% CI, 0.9–1.9; $P = 0.19$) for 30 applications per
month. When stratified by history of perineal use of talc (yes/no) and history of tubal
ligation or hysterectomy (yes/no), women who had used talc perineally and but had not
undergone surgery for sterilization had the highest risk for ovarian cancer (odds ratio, 1.3;
95% CI, 0.9–2.0). [Limitations of this study included the lack of information on talc use.]

Booth *et al.* (1989) reported results of a hospital-based case–control study of the risk
for ovarian cancer conducted in 15 hospitals in London and Oxford (United Kingdom)
from October 1978 to February 1983. Women aged 65 years or under at diagnosis and
who were diagnosed within 2 years of the study interview were eligible for inclusion. A
total of 280 potential cases were identified, interviewed and classified with respect to
tumour histology. After excluding 45 women, 235 cases were included in the analysis. A
total of 451 controls with the same age distribution as the cases were selected from the
same 15 hospitals. Controls had a range of admission diagnoses; gastrointestinal disease
($n = 105$) and bone or joint disease ($n = 70$) were the most common. Women were
excluded as controls if they had a history of bilateral oophorectomy or if they had a
condition related to oral contraceptive use or other reproductive factors. Participation rates
were not provided. Interviewers used a standard questionnaire to obtain information on
reproductive and menstrual history, as well as exposure to exogenous estrogens, cigarettes
and talc. Talc exposure was categorized according to the frequency of perineal use (never,
rarely, monthly, weekly or daily) and whether it was used for storage of a diaphragm.
Multiple logistic regression adjusted for age and socioeconomic status was conducted.
Fifty-seven cases [24.3%] and 77 controls [17.1%] reported a history of weekly use of
talc in the genital area, while 71 cases [30.2%] and 139 controls [30.8%] reported daily
use. Weekly genital use of talc was associated with a significantly increased risk for
ovarian cancer (odds ratio, 2.0; 95% CI, 1.3–3.4), while daily use was associated with a
non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.8–1.9), after adjustment for age
and socioeconomic status. The *p*-value for trend with increasing frequency of use was of
borderline significance ($P = 0.05$). The percentage of diaphragm users who reported
storing their diaphragm in talc was not significantly different between the cases (86%)
and controls (81%). [Limitations of this hospital-based study included the limited
information on talc use. As participation rates were not provided, the possibility of
selection bias is difficult to evaluate. Although covariates such as oral contraceptive use
or parity were available, it was not explicitly stated if they were evaluated.]

Harlow and Weiss (1989) conducted a study of perineal use of powder and the risk
for borderline ovarian cancer in western Washington State, USA. Cases were
116 Caucasian women aged 20–79 years who had been diagnosed with borderline serous
or mucinous epithelial ovarian cancer between 1980 and 1985, and who were identified
by International Classification of Diseases-0 codes obtained from a population-based

cancer-reporting system. Controls were identified from the same counties of residence by random-digit dialling. A total of 158 women with a similar age distribution to the cases and who had not undergone a bilateral oophorectomy were included in the analysis. Cases and controls were interviewed in-person to obtain information on reproductive, sexual and medical histories, as well as on perineal exposure to talc (through multiple open-ended questions about the history of powder use of the participant). Among all eligible cases and controls identified for the study, 68% of the cases and 74% of the controls were interviewed. The authors controlled for age (20–39, 40–59 or 60–79 years), parity (nulliparous or parous) and oral contraceptive use (ever/never). Exposure to talc was broadly categorized as 'any perineal use of dusting powders' (after bathing, on sanitary napkins or for diaphragm storage) and further subcategorized according to method of use (diaphragm storage only, after bathing only, sanitary napkins only, after bathing and on sanitary napkins and specific combinations of the various methods) and type of powder used (cornstarch only, baby powder only, talc unspecified (no combined use), deodorizing powder only or combinations of powders). Forty-nine cases [42.2%] and 64 controls [40.5%] reported a history of 'any perineal exposure to powder' to yield an odds ratio of 1.1 (95% CI, 0.7–2.1). When analysed by the type of powder used, the risk for borderline ovarian cancer was elevated only for perineal use of deodorizing powder alone (odds ratio, 3.5; 95% CI, 1.2–28.7) or in combination with other powders (odds ratio, 2.8; 95% CI, 1.1–11.7). No association was noted for the use of baby powder alone (odds ratio, 0.8; 95% CI, 0.4–1.9) or for combined use (odds ratio, 0.9; 95% CI, 0.5–2.0) or for other unspecified use of talc (odds ratio, 1.0; 95% CI, 0.4–2.4). No significant association was found between risk for borderline tumours and any individual method of powder use, including use after bathing, on sanitary napkins or for diaphragm storage. The authors reported no increase in risk with increasing number of days of powder use, although the data were not provided in the paper. [Limitations of this study included the incomplete information on powder use and its small size.]

Chen *et al.* (1992) (described in detail in Section 2.1.2) conducted a case–control study in Beijing, China, of several risk factors for epithelial ovarian cancer that included perineal exposure to talc (yes/no use of dusting powder to the lower abdomen or perineum for 3 or more months). The analysis was carried out on 112 newly diagnosed cases identified between 1984 and 1986 through the Beijing Cancer Registry and 224 age-matched community controls (two controls per case). Seven cases [6.3%] and five controls [2.2%] reported use of talc-containing powders which resulted in an odds ratio of 3.9 (95% CI, 0.9–10.6) after adjustment for education and parity. [The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases that were excluded due to death and the exclusion of controls who had a history of serious health problems (which may have resulted in selection bias), the limited information on perineal use of talc, the lack of adjustment for other potential confounding variables, the small number of cases and the low prevalence of talc use.]

TALC   365

Harlow *et al.* (1992) analysed perineal exposure to talc and the risk for ovarian cancer among 235 cases and 239 controls in the Boston, MA metropolitan area (USA). Cases were diagnosed with ovarian cancer between June 1984 and September 1987 at one of 10 Boston hospitals and controls were identified from town registers listing the name, age and address of all residents in Massachusetts. All cases were Caucasian women aged 18– 76 years at diagnosis and were similar to the controls with respect to race, age and area of residence. Of 397 cases identified during the study period, 31% were not interviewed due to physician and/or patient refusal, death or change of address. After excluding women whose cancer diagnosis was not confirmed by an independent pathology review [9.4% of eligible cases], 235 women were included in the analysis. A total of 526 women were contacted as potential controls. Of these, 239 [45.4%] were interviewed, 25% could not be reached, 10% reported a previous bilateral oophorectomy and 19% did not wish to participate in the study. In-person interviews were conducted with cases and controls to obtain information on occupational history, medical and reproductive histories, dietary history, cigarette smoking and hygienic practices (use of douches, types of sanitary protection used, perineal exposure to talc). Exposure to talc was categorized on the basis of 'any' exposure, the method of application (dusting on sanitary napkins and/or underwear, via partner or application to diaphragm, dusting on perineum), the brand used, age at first use, duration and frequency of use. Total lifetime exposure to talc was estimated by cumulating the frequency of exposure and years of use to arrive at a summary measure of the total number of applications (< 1000, 1000–10 000, > 10 000). Covariates evaluated as potential confounders included age, education, marital status, religion, weight, use of oral contraceptives and parity; of these, age, education (< 12 years, > 12 years), marital status (never/ever), religion (Jewish, non-Jewish), weight (< 140 lb, ≥ 140 lb) and parity (0, 1–2, > 2) were included in all multivariable models. A history of 'any' perineal exposure to talc-containing powders was reported by 48.5% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.0–2.1). When the method of application was examined, only direct application to the perineum as a dusting powder was associated with a significant increase in risk (odds ratio, 1.7; 95% CI, 1.1– 2.7). Women who reported at least 30 applications of talcum powder per month had a significant increase in risk (odds ratio, 1.8; 95% CI, 1.1–3.0), while women with fewer applications per month did not. A significant positive trend was seen with number of monthly applications ($P = 0.046$). Women with at least 10 years of perineal exposure had a borderline significant increase in risk (odds ratio, 1.6; 95% CI, 1.0–2.7) and the *p*-value for trend was also of borderline significance ($P = 0.07$). Analyses stratified by age at first use indicated that women who first used talc genitally before the age of 20 years had the highest risk (odds ratio, 1.7; 95% CI, 1.1–2.7); those stratified by years since last use suggested that women with the most recent perineal use of talc (within the previous 6 months) had the highest risk (odds ratio, 2.3; 95% CI, 1.3–4.0). In an analysis stratified by use before versus after 1960, women who reported some perineal use of talc before 1960 had a significantly elevated risk for ovarian cancer (odds ratio, 1.7; 95% CI, 1.1– 2.7), while women with exclusive genital use of talc after 1960 did not (odds ratio, 1.1;

95% CI, 0.6–2.1). Women who had used more than 10 000 lifetime applications had a borderline significant increase in risk (odds ratio, 1.8; 95% CI, 1.0–3.0). This was unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0). However, when use of talc during non-ovulatory periods and after surgical sterilization was excluded, the increase in risk associated with more than 10 000 lifetime applications was significant (odds ratio, 2.8; 95% CI, 1.4–5.4). In analyses of each histological type and grade, the strongest associations were seen for endometrioid tumours (odds ratio, 2.8; 95% CI, 1.2–6.4) and tumours of borderline invasiveness (odds ratio, 2.4; 95% CI, 1.2–4.5) (Table 2.4).

Rosenblatt *et al.* (1992) conducted a hospital-based case–control study among 77 women who were hospitalized at Johns Hopkins Hospital in Baltimore, MD (USA) for ovarian cancer (cases) and 46 who were hospitalized for non-gynaecological, non-malignant conditions (controls). The cases were newly diagnosed with pathologically confirmed epithelial ovarian cancer between 1981 and 1985, the majority of whom were aged 40–69 years. Of 140 eligible cases, 108 (77.1%) were interviewed. Thirteen were subsequently excluded because no control was identified and 18 were excluded for an unspecified reason. Controls were matched to cases by age, race and date of diagnostic admission. Information on genital and respiratory exposure to fibre-containing substances (talc, asbestos and fibreglass), as well as potential confounders, was collected using a structured questionnaire which was administered in the hospital and by telephone. Covariates that were considered to be potential confounders included tobacco use, 'ovulatory time period', parity, family history of cancer, obesity, education, education of husband, previous history of cancer, marital status, religion and the use of oral contraceptives and other methods of contraception. Sources of genital fibre exposure (yes/no) included diaphragm use and dusting of either the perineum or sanitary napkins with talcum powder. Potential sources of respiratory fibre exposure (yes/no) included use of face or body powders containing talc, insulation installed at residence and living in the vicinity of or employment in a fibre-emitting industry (such as shipyard, asbestos or talc mine, asbestos/talc/fibreglass processing plant). A large percentage of both the cases (87%) and controls (88%) reported exposure to genital fibre, with an odds ratio of 1.0 (95% CI, 0.2–4.0) after adjustment for parity. A long duration of genital fibre use (median duration, ≥ 37.4 years) was associated with a borderline significant increase in the risk for ovarian cancer (odds ratio, 2.4; 95% CI, 1.0–5.8) after adjustment for religion. Odds ratios were also calculated for genital use of bath talc (odds ratio, 1.7; 95% CI, 0.7–3.9), use of talc on sanitary napkins (odds ratio, 4.8; 95% CI, 1.3–17.8) and use of talc on a diaphragm (odds ratio, 3.0; 95% CI, 0.8–10.8). No association was observed between risk for ovarian cancer and history of previous gynaecological or abdominal surgery that may have resulted in peritoneal exposure to talc. [Limitations of this study included the very small number of cases and controls, the broad definition of fibre exposure used in certain exposure variables and the limited information on perineal exposure to talc.]

Tzonou *et al.* (1993) conducted a hospital-based case–control study of risk factors for epithelial ovarian cancer in the Greater Athens region of Greece. The cases were 189 women

Table 2.4. Perineal talc use and ovarian cancer risk: by tumour histology

References	No. of cases	Histology	Relative risk[a] (95% CI)
Harlow *et al.* (1992)	60	Serous[b]	1.4 (0.9–2.2)
	17	Mucinous	1.2 (0.6–2.5)
	18	Endometrioid	2.8 (1.2–6.4)
Chang & Risch (1997)	254	Serous[b]	1.3 (1.0–1.9)
	80	Mucinous	1.6 (1.0–2.6)
	74	Endometrioid	1.7 (1.0–2.8)
Cook *et al.* (1997)	131	Serous	1.7 (1.1–2.5)
	43	Mucinous	0.7 (0.4–1.4)
	36	Endometrioid	1.2 (0.6–2.3)
Cramer *et al.* (1999)	229	Serous invasive	1.7 (1.2–2.4)
	83	Mucinous	0.8 (0.4–1.4)
	130	Endometrioid/clear cell	1.0 (0.7–1.6)
Wong *et al.* (1999)	136	Serous	1.2 (0.7–2.1)
	11	Mucinous	1.5 (0.6–4.0)
	21	Endometrioid	1.4 (0.7–2.7)
Gertig *et al.* (2000)	76	Serous invasive	1.4 (1.0–1.9)
Mills *et al.* (2004)	42	Serous invasive	1.8 (1.1–2.8)
	10	Mucinous invasive	2.6 (0.9–7.4)
	14	Endometrioid	1.3 (0.6–2.6)

CI, confidence interval
[a] Any or ever use of talc
[b] Includes borderline and invasive serous tumours

TALC

under 75 years of age who underwent surgery for ovarian cancer at one of two cancer hospitals in Athens between June 1989 and March 1991. The controls were 200 women under 75 years of age who were residents of Greater Athens and who visited patients hospitalized in the same wards as the cases during the study period. Ninety per cent of the eligible cases and 94% of the eligible controls agreed to participate. In-hospital interviews were conducted to collect information on a range of demographic, socioeconomic and reproductive factors, as well as information on exposure to hair dyes, analgesics, tranquilizers and talc. Exposure to talc was assessed qualitatively as 'yes/no' application of talc in the perineal region. In multivariable analyses, models were adjusted for age in 5-year groups, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking status, alcohol use, coffee consumption and the other exposures of interest (use of analgesics, tranquilizers and hair dyes). Application of talc to the perineal region was reported by six cases [3.2%] and seven controls [3.5%] to yield an odds ratio of 1.1 (95% CI, 0.3–4.0) after adjustment for the potential confounders. [Limitations of this hospital-based case–control study included the very low prevalence of perineal use of talc.]

Purdie *et al.* (1995) conducted a case–control study among women in the three most populous Australian states—Queensland, New South Wales and Victoria. Cases were women, aged 18–79 years, who had been diagnosed with epithelial ovarian cancer between August 1990 and December 1993 at gynaecological oncology treatment centres in one of these three regions. Women were excluded if they had a metastatic tumour, were outside the eligible age range, could not be contacted, were too ill or were incapable of completing the questionnaire in conjunction with a trained interviewer (because of language difficulties or psychiatric conditions). Each case was confirmed by an independent pathological review of tissue specimens. Of 1116 cases identified during the study period, 201 (18%) were ineligible (e.g. due to a non-ovarian primary cancer or age at diagnosis). Among the 915 eligible cases, 824 (90%) agreed to participate and were interviewed. Reasons for non-participation included death before interview (50 cases), patient refusal (34 cases) and physician refusal (seven cases). Controls were identified from the electoral roll and were similar to the cases in age distribution and area of residence. Women were excluded as a control if they had a history of ovarian cancer or bilateral oophorectomy, could not be reached or could not complete the questionnaire. Among 1527 potential controls identified from the electoral roll, 1178 were located and found to be eligible (77%). Of these, 860 agreed to participate in the study (73% of the eligible controls). Reasons for ineligibility among the controls included failure to locate the individual (192), inability to complete the questionnaire due to language difficulties, a psychiatric condition, illness or death (105), previous bilateral oophorectomy (48) and age (four). Trained interviewers used a standardized questionnaire to collect information on medical, reproductive, family and occupational histories, as well as data on dietary factors and history of talc use. Questionnaires were administered face-to-face either in the clinic (for cases) or in the home of participant (for some cases and all controls). Covariates evaluated as potential confounders included parity, hysterectomy, tubal ligation, duration

of oral contraceptive use, age, education, body mass index, tobacco smoking status, family history of cancer and multiple menstrual and reproductive factors. Talc use around the abdomen or perineum was reported by 56.7% of cases and 52% of controls to yield an odds ratio of 1.3 (95% CI, 1.0–1.5) after adjustment for parity. Although enrolment in the electoral roll is mandatory in Australia, the authors determined that 28 cases [3.4%] had never enrolled and the enrolment status could not be confirmed for 46 cases [5.6%]. The results did not change when the analyses were limited to cases with confirmed enrolment in the electoral role.

Green *et al.* (1997) evaluated the association between tubal ligation or hysterectomy and the risk for ovarian cancer using the Australian study population described by Purdie *et al.* (1995). [The analysis by Green *et al.* (1997) used the same number of cases but five fewer controls than Purdie *et al.* (1995).] Duration of talc use was calculated as age at first reported use until age at occurrence of the earliest of any of the following events: surgical sterilization, reported last use of talc, diagnosis or interview. A modest increase in risk for ovarian cancer was observed with peritoneal use of talc (odds ratio, 1.3; 95% CI, 1.1–1.6). Neither duration of talc use nor age at first use were associated with risk for ovarian cancer, although the relative risks (95% CI) were not provided and the duration categories evaluated were not specified. When compared with women with no history of genital exposure to talc and patent fallopian tubes, women with a history of talc use and no history of surgical sterilization had the highest risk for ovarian cancer (odds ratio, 1.3; 95% CI, 1.0–1.7), while women with a history of tubal ligation or hysterectomy and no talc use had the lowest risk (odds ratio, 0.6; 95% CI, 0.5–0.8). [The primary limitation of this study was the restricted information on perineal use of talc.]

Shushan *et al.* (1996) examined the association between exposure to fertility drugs and the risk for ovarian cancer among 200 cases of epithelial ovarian cancer (164 invasive and 36 borderline) and 408 controls. All participants were living in Israel and were 36–64 years of age at enrolment into the study. Cases were identified through the Israel Cancer Registry from January 1990 to September 1993. Among 287 women who met the eligibility criteria (histologically confirmed diagnosis, cancer diagnosed and reported during study period, born between 1929 and 1957 and alive at time of interview), 87 (30.3%) were excluded because of inability to locate the patient or physician (25%), illness (1%), refusal by the physician (1%) or refusal by the patient (3%). Controls were identified by random-digit dialling and were matched to the cases by geographical area. Women were eligible to be included as a control if they were born in the same period as the cases. Potential controls were excluded if they had a history of bilateral oophorectomy (1%). Of 2072 telephone calls that successfully reached a household member, approximately half of the households [47.8%] contacted had a potentially eligible woman who was at home. Of these, 16.2% refused to participate and 10.7% were excluded because the woman did not speak Hebrew. Trained interviewers administered a standard questionnaire to all cases and controls. The questionnaire collected detailed information on reproductive history, use of oral contraceptives and fertility drugs, as well as exposure to talc (never/seldom, moderate/a lot). Although the main association of interest was use

of fertility drugs and the risk for ovarian cancer, the authors reported that 21 cases (10.5%) and 23 controls (5.6%) had a history of moderate or frequent use of talc, which yielded an unadjusted odds ratio of [1.97] ($P = 0.04$). [Limitations of this study included the very sparse information on talc use and the unavailability of adjusted results for the association between use of talc and the risk for ovarian cancer.]

Chang and Risch (1997) analysed the association between perineal use of powder and the risk for ovarian cancer among 450 cases and 564 population controls from metropolitan Toronto and southern Ontario, Canada. Cases were diagnosed between November 1989 and October 1992 and were between the ages of 35 and 79 years at entry into the study. Of 631 cases identified during the study period, 71.3% (450) were interviewed and included in the analysis. Reasons for non-participation included death (8.7%), physician refusal (4.6%), severe illness (4.8%), loss to follow-up (2.7%) and patient refusal (7.9%). Potential controls were identified through records of the Ontario Ministry of Finance based on their residence and age, were matched to cases within 15-year age groups and were excluded from the study if they had a history of bilateral oophorectomy more than 1 year before entry into the study. Among 873 eligible controls identified, 309 [35.4%] did not participate. Reasons included participant refusal (30.2%), illness (1.9%) or loss to follow-up (3.2%). Interviewers administered a standard questionnaire during an in-home interview to obtain information on the history, frequency and duration of use of talcum and cornstarch powder, as well as multiple medical and reproductive covariates of interest. Talc exposure was categorized on the basis of 'any' exposure in the perineal area, on the method of application (directly to the perineum after bathing or showering, dusting on sanitary napkins), on the frequency of application (< 10, 10–25, > 25 applications per month) and on the duration of exposure (< 30, 30–40, > 40 years of use). Multiple logistic regression was used in the analyses, with adjustment for age, duration of oral contraceptive use, parity (defined as the number of full-term pregnancies), duration of lactation for each pregnancy, history of tubal ligation or hysterectomy and family history of breast or ovarian cancer. Forty-four per cent of cases and 36% of controls reported 'any' talc use in the perineal area to yield an odds ratio of 1.4 (95% CI, 1.1–1.9). Among the specific types of talc exposure, application to the perineum after bathing was associated with a borderline significant increase in risk (odds ratio, 1.3; 95% CI, 1.0–1.7), while application on sanitary napkins (a less common use in this study population) was associated with an elevated but non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.9–2.0). A borderline significant trend was seen with increasing duration of exposure to talc (odds ratio per 10 years of exposure, 1.1; 95% CI, 1.0–1.2), but not with increasing frequency of exposure. An analysis of duration by category (< 30, 30–40, > 40 years) did not suggest a dose–response relationship (odds ratios of 1.0; 1.7; 95% CI, 1.1–2.6; 1.4; 95% CI, 1.0–2.2 and 0.9; 95% CI, 0.5–1.4, respectively). Use of cornstarch in the perineal area, either alone or in conjunction with occasional talc, was not associated with the risk for ovarian cancer, although prevalence of use was low (less than 2% of subjects). To evaluate exposure pre- and post-1970, as well as exposure pre- and post-tubal ligation or hysterectomy, the authors assumed that participants initiated

perineal use of after-bath talc at the age of 20 years. A similar, non-significantly elevated, risk for ovarian cancer was seen for use pre- and post-1970. A higher odds ratio was seen for use of after-bath talc before tubal ligation or hysterectomy (odds ratio, 1.1; 95% CI, 1.0–1.2) than for use after these surgical procedures (odds ratio, 1.0; 95% CI, 0.8–1.3). These estimates did not change when different starting ages, between 15 and 24 years, were used in the analysis. The authors also evaluated the association between perineal use of talc and invasive and borderline cancers separately, and found that the risk was elevated for both tumour types but was significant only for invasive tumours. In addition, risk was similar across the major histological subtypes of ovarian cancer (serous, mucinous, endometrioid) (see Table 2.4). [Limitations of this study included the lack of information on use of talc.]

Cook *et al.* (1997) evaluated the association between use of genital powders or deodorants and the risk for ovarian cancer in a case–control study conducted in three counties of western Washington State, USA. Cases were aged 20–79 years at diagnosis, were diagnosed with borderline or invasive epithelial ovarian cancer between 1986 and 1988 and were identified using the population-based Cancer Surveillance System of western Washington. Controls were identified using random-digit dialling, were residents of the three counties of interest and were similar in age to the cases. Among 512 eligible cases identified, 329 were interviewed (64.3%) and 313 were included in the analysis [61.1%]. A total of 183 eligible cases were not interviewed due to death (104), physician or patient refusal (73) or loss to follow-up (six). An additional 16 cases who were interviewed were excluded from the analysis because of non-white race (seven) and unknown genital use of powder (nine). Among 721 women identified as potential controls, 521 were interviewed (72.3%) and 422 were included in the analysis [58.5%]. Reasons for excluding interviewed controls from the analysis included: non-white race (28), age greater than 79 years (five), history of bilateral oophorectomy (58), unknown oophorectomy status (four) and unknown genital use of powder (four). Information on powder use, including the type, method, frequency and duration of use, and the covariates of interest was collected during in-person interviews. Covariates considered to be potential confounders in multivariable analyses included age, education, income, marital status, body mass index, oral contraceptive use and parity. A history of 'any' lifetime genital powder use (perineal dusting, diaphragm storage, use on sanitary napkins or use of deodorant spray) was reported by 50.8% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.1–2.0) after adjustment for age. Among the individual methods of genital use of powder, risk was significantly elevated only for exclusive perineal dusting (odds ratio, 1.8; 95% CI, 1.2–2.9) after adjustment for age. In analyses adjusted for age and other types of genital use of powder, both perineal dusting (odds ratio, 1.6; 95% CI, 1.1–2.3) and genital deodorant spray (odds ratio, 1.9; 95% CI, 1.1–3.1) were associated with risk for ovarian cancer, while use of powder on a diaphragm or on sanitary napkins was not associated with an increased risk. There was no evidence of an increasing trend in risk with greater duration of perineal dusting, but a significant positive trend was noted for both duration (odds ratio, 2.7; 95% CI, 1.1–6.6 for > 12 cumulative lifetime months; *p* for

trend < 0.05) and number of lifetime applications (odds ratio, 2.6; 95% CI, 0.9–7.6 for > 500 lifetime applications; *p* for trend < 0.05) of genital deodorant spray. The effect estimates did not change materially when perineal use of dusting powder after the date of tubal ligation or hysterectomy was excluded. Risk was significantly elevated among women with any history of perineal dusting before 1976 (odds ratio, 1.8; 95% CI, 1.1–2.9), but the authors were unable to evaluate risk for use exclusively after 1976 due to the small number of women (four cases and 10 controls) who had had this exposure. Among the individual types of powder evaluated (cornstarch, talcum powder, baby powder, deodorant powder, scented body/bath powder), risk for ovarian cancer was non-significantly elevated for 'any' use of talcum powder (odds ratio, 1.6; 95% CI, 0.9–2.8) and bath/body powder use (odds ratio, 1.5; 95% CI, 0.9–2.4) after adjustment for age and other types of powder use (yes/no). The authors also evaluated the association between any genital use of powder and the risk for the major histological subtypes of ovarian cancer (see Table 2.4). Risk was significantly elevated for serous tumours (odds ratio, 1.7; 95% CI, 1.1–2.5) and all other tumour types (odds ratio, 1.8; 95% CI, 1.1–2.8) but not for mucinous or endometrioid tumours. [Limitations of this study included the relatively low participation rates among the cases and controls.]

Eltabbakh *et al.* (1998) compared risk factors among 50 cases of primary extra-ovarian peritoneal carcinoma (the 'study' group) and 503 cases of primary epithelial ovarian cancer (the 'control' group) treated at Roswell Park Cancer Institute in Buffalo, NY (USA), between October 1982 and October 1996. No healthy controls were enrolled in this study. Diagnoses were reviewed by staff in the Division of Pathology (study and control groups) and were confirmed by a single pathologist as part of another study (study group only). Information on reproductive history, menstrual history, use of hormones and contraceptives and personal hygiene was collected through a self-administered, 44-item questionnaire which all patients were asked to complete during the hospital admission process. All women who returned a questionnaire were eligible to be included in the study. Among these patients, the overall questionnaire response rate was 60%. Response was inversely correlated with severity of disease and response rates were similar for the two diagnoses included in this study. Because data on perineal talc use was missing for 37 patients in the 'control' group, only 466 ovarian cancer patients were included in the analysis. Women who had primary ovarian cancer were significantly more likely to report a history of perineal use of talc compared with women who had primary peritoneal cancer (48.1% versus 26.0%; [crude odds ratio = 2.6] *P* = 0.003). Among the other characteristics examined, only age and age at menarche differed significantly in the two groups. [Limitations of this study included the minimal information on talc use, the low questionnaire response rate among study participants, particularly among the patients with more advanced disease, the use of a self-administered questionnaire completed during the admissions process, which may have limited the quality of the responses, and the lack of a 'healthy' comparison group.]

Godard *et al.* (1998) evaluated risk factors for familial and sporadic ovarian cancer in a population of French Canadian women in Montréal, Quebec (Canada). Of 231 cases

who were identified between 1995 and 1996 at two gynaecological oncology clinics in Montréal, 183 (79.2%) were interviewed and 170 (73.6%) were included in the analysis. Reasons for non-inclusion were death ($n = 21$), refusal/unavailability to participate ($n = 12$), loss to follow-up ($n = 15$) and tumours were non-epithelial in origin ($n = 13$). All cases were between the ages of 20 and 84 years at diagnosis, with a mean age at diagnosis of 53.7 years and a mean age at interview of 55.9 years. Controls were identified using a modified random-digit dialling method and were frequency-matched to cases by age (within 1 year) and French Canadian ethnicity. The mean age at interview for the controls was 56.7 years. Among 750 households contacted regarding participation in the study, 66.7% ($n = 500$) either did not have an eligible female resident or did not reply to the researchers' inquiries and 10.7% refused to participate. A total of 170 women were interviewed and included in the analysis as controls. A standardized 57-item questionnaire was used to obtain information on the family, medical and reproductive history of each participant. Cases were interviewed either by telephone (30%) or in the study clinics (70%). No information was given on the methods of interview for control subjects. Information on family history of cancer was collected to determine whether risk factors differed for the sporadic and familial cases of ovarian cancer. Familial cases were those patients who had one or more family members (first, second or third degree relatives) with breast cancer diagnosed before 55 years of age or ovarian cancer diagnosed at any age. Sporadic cases were those patients who had no family members with breast cancer diagnosed before 55 years of age or with ovarian cancer diagnosed at any age. Perineal exposure to talc was assessed qualitatively (ever/never, with 'never' as the baseline). Covariates that were considered to be potential confounding variables were age at menarche, age at menopause, parity, age at first and last childbirth, duration of oral contraceptive use, age at last oral contraceptive use, tubal ligation, alcohol use and previous breast or abdominal surgery. Talc exposure was more common in cases than controls, with 10.6% of the cases and 4.7% of the controls reported perineal use of talc ($P = 0.06$). No difference between perineal use of talc was reported in the familial and sporadic cases ($P = 0.79$). Multivariate analyses were performed comparing all cases, (all, sporadic, familial) with controls. In these analyses, perineal use of talc was associated with a non-significant increase in the total risk for ovarian cancer (odds ratio, 2.5; 95% CI, 0.9–6.6; $P = 0.07$). Risk was similarly non-significantly elevated for sporadic (odds ratio, 2.5; 95% CI, 0.9–7.1) and familial cases (odds ratio, 3.3; 95% CI, 0.9–12.4) compared with the controls. [Limitations of this study included its small size and the lack of any detailed information on perineal use of talc. The control participation rates may have been low (although this is not clear) and it is not certain how representative the controls were.]

Cramer *et al.* (1999) analysed the association between genital exposure to talc and the risk for primary epithelial ovarian cancer among 563 cases and 523 controls residing in eastern Massachusetts and New Hampshire, USA. Cases were identified between May 1992 and March 1997 through hospital tumour boards or statewide cancer registries. Among 1080 cases diagnosed in this period (including borderline tumours), 203 (18.8%)

were excluded due to death, change of address, inability to speak English, no telephone in residence or a non-ovarian primary cancer. Of the 877 eligible cases remaining after these exclusions, 563 (64%) were included in the analysis. The remaining 314 cases were excluded because of physician refusal ($n = 126$) and patient refusal ($n = 136$). Pathology reports were reviewed to confirm the diagnoses for all cases, and slides were requested and reviewed in the case of discrepancies between the reported histology and the histology assigned based on the pathology report review. Controls were identified by random-digit dialling and town resident books (to identify additional women over the age of 60 years who lived in Massachusetts) and were frequency-matched to cases by age (within 4 years) and location of residence. Of the potentially eligible controls, 72% of those identified by random-digit dialling and 49% of those identified through town books agreed to participate. All study participants were interviewed in-person using a standardized questionnaire to obtain information on their medical and reproductive histories, family history and personal habits. The questionnaire also asked multiple questions on powder use, including route of exposure (application to non-genital areas, application to perineum, sanitary napkins or underwear, husband's use of powders in his genital area), brand of powder used (talc, cornstarch), age at first use, duration and frequency of use (< 30, $30–39$, > 40 uses per month). Participants were asked about exposures that occurred at least 1 year before the date of diagnosis (cases) or the date of interview (controls). The results were adjusted for the following potential confounding variables: age, state of residence, body mass index, parity, oral contraceptive use, family history of breast or ovarian cancer and history of tubal ligation. The prevalence of talc use was higher among cases than controls; 44.6% of cases and 36.1% of controls reported 'any' use of talc (included use in both genital and non-genital areas) and 27.0% of cases and 18.2% of controls reported 'genital' use of talc (included dusting of perineum/sanitary napkins/underwear, either exclusively or in combination). Talc use in non-genital areas was not associated with risk when compared with women who did not use personal powder (odds ratio, 1.1; 95% CI, 0.8–1.5). However, genital use of talc was associated with a significant 60% increase in risk (odds ratio, 1.6; 95% CI, 1.2–2.2). Women who reported more than one method of talc use in the genital area had an even greater risk for ovarian cancer (odds ratio, 2.2; 95% CI, 1.3–3.6). No association was observed between genital use of talc and risk for ovarian cancer among women who had undergone tubal ligation after adjustment for age (odds ratio, 1.0; 95% CI, 0.5–2.1). Because of the low prevalence of use ($< 1\%$ of the study population) of cornstarch, evaluation of this product was uninformative. When women who had been exposed to powder only in non-genital areas were excluded from the analysis, no linear trend was observed between risk for ovarian cancer and age at first genital use of talc, duration of use, frequency of use or total number of lifetime applications. However, when non-genitally exposed women were included in the analysis, a significant linear trend was observed with increasing number of lifetime applications, after talc applications that occurred during non-ovulatory years or after tubal ligation or hysterectomy were excluded ($P = 0.02$). Additional findings of interest included: a non-significant increase in risk among married women with no

personal talc use whose husbands had used talc for genital hygiene (odds ratio, 1.5; 95% CI, 0.9–2.5); and a stronger association between genital use of talc and risk for ovarian cancer among women who had used talc before their first live birth (odds ratio, 1.6; 95% CI, 1.1–2.3) than for women who had used it exclusively after their first live birth (odds ratio, 1.0; 95% CI, 0.4–2.5). The association with genital use of talc was strongest for serous invasive tumours (odds ratio, 1.7; 95% CI, 1.2–2.4). No association was observed for endometrioid/clear-cell (odds ratio, 1.0; 95% CI, 0.7–1.6) or mucinous tumours (odds ratio, 0.79; 95% CI, 0.4–1.4) (see Table 2.4).

Wong *et al.* (1999) reported the results of a case–control study conducted at Roswell Park Cancer Institute, Buffalo, NY (USA) of 499 cases treated between October 1982 and October 1992 (largely those reported by Eltabbakh *et al.*, 1998) and 755 hospital-based controls. The controls were randomly selected from a registry of patients who were being treated for non-gynaecological malignancies and were frequency-matched to cases by age at diagnosis (within 5 years). The most common diagnoses among controls were colorectal (43.3%) and skin cancers (34.5%) and leukaemia (17.7%). All participants completed the self-administered, 44-item questionnaire that all patients were asked to complete during the hospital admission process. All analyses were adjusted for age at diagnosis, parity, oral contraceptive use, tobacco smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location and history of tubal ligation or hysterectomy. The analysis was restricted to 462 cases and 693 controls with information on perineal use of talc. 'Ever' use of talc (genital or non-genital) was reported by 47.8% of the cases and 44.9% of the controls, while use of talc in the genital or thigh area was reported by 34.0% of the cases and 32.2% of the controls. There was no association between any method of talc use and the risk for ovarian cancer after adjusting for several potentially confounding variables. The adjusted odds ratio for talc use in the genital or thigh area was 1.0 (95% CI, 0.8–1.3). Duration of talc use was similar in the cases and controls, and no association between talc use and the risk for ovarian cancer was found for any duration category. No significant association was observed between talc use and any of the major histological subtypes of ovarian cancer (see Table 2.4); the odds ratio for serous cystadenocarcinoma was 1.2 (95% CI, 0.7–2.1). No evidence was found of effect modification by history of tubal ligation or hysterectomy. Among women who had not undergone tubal ligation or hysterectomy, the odds ratio for the association between talc use and risk for ovarian cancer was 1.2 (95% CI, 0.8–1.6) while among women who had undergone tubal ligation or hysterectomy, the odds ratio was 0.8 (95% CI, 0.5–1.2). [Limitations of the study included the sparse information on talc use. In addition, the use of hospital controls with non-gynaecological malignancies may have caused selection bias. As noted in the earlier report by Eltabbakh *et al.* (1998), the response rate to the questionnaire was low in this study population, particularly among the patients with more advanced disease.]

Ness *et al.* (2000) examined whether factors related to an inflammatory response of the ovarian epithelium (such as exposure to talc, endometriosis, cysts and hyperthyroidism) played a role in the risk for ovarian cancer. The study was conducted

among 767 recently diagnosed cases of epithelial ovarian cancer and 1367 population-based controls. Cases were aged 20–69 years and were identified between 1994 and 1998 at 39 hospitals in the Delaware Valley region (USA). Of 1253 potentially eligible cases, 61.2% were interviewed and included in the analysis. Reasons for excluding women from the study included: diagnosis more than 6 months before the interview ($n = 296$), severe illness or death ($n = 69$), unavailability of contact information ($n = 15$), physician refusal ($n = 14$) or patient refusal ($n = 92$). Controls were identified through random-digit dialling (for controls ≤ 65 years of age) and Health Care Financing Administration lists (for controls 65–69 years of age) and were frequency-matched to cases by age and location of residence. Overall, 72% of the eligible potential controls agreed to participate in the study. A pathological review was conducted for a subset of the cases ($n = 120$). When compared with the original diagnosis, the central review was 95% concordant for invasiveness and 82% concordant for cell type. The original pathological diagnosis was used in the analysis for all cases. A standardized, 1.5-hour interview was conducted in the homes of the participants to collect information on menstrual and reproductive history, sexual activity, use of contraceptives, history and duration of talc use (genital and non-genital applications and exposure via male sexual partners). Talc use was categorized according to the method of application (never, feet, genital/rectal, sanitary napkins, underwear, diaphragm or cervical cap, or male partner) and duration of exposure (< 1 year, 1–4 years, 5–9 years, > 10 years). Unconditional logistic regression adjusted for age, parity, race, family history of ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy and lactation was used in all analyses. A history of talc use in the genital/rectal area was reported by 161 cases [21.0%] and 219 controls [16.0%] to yield an adjusted odds ratio of 1.5 (95% CI, 1.1–2.0). Significant associations were also observed for the use of talc on sanitary napkins (odds ratio, 1.6; 95% CI, 1.1–2.3) and on underwear (odds ratio, 1.7; 95% CI, 1.2–2.4). The use of talc on the feet, arms or breasts was associated with a significant 40% increase in risk; however, women may also have used talc on more than one area of the body, including the genital and/or rectal area. Use of talc on diaphragms or cervical caps and use by a male sexual partner were not associated with the risk for ovarian cancer. There was no clear trend between risk for ovarian cancer and increasing duration of use of talc on the genital and/or rectal area or feet. Adjusted odds ratios of 2.0 (95% CI, 1.0–4.0), 1.6 (95% CI, 1.1–2.3), 1.2 (95% CI, 0.8–1.9) and 1.2 (95% CI, 1.0–1.5) were observed for < 1 year, 1–4 years, 5–9 years and ≥ 10 years of use, respectively. [Limitations of this analysis included the sparse information on talc use. In analyses of duration, the use of talc on the feet was also included as an exposure. The relatively low participation rates among cases was also a limitation of the study.]

Langseth and Kjaerheim (2004) (described in detail in Section 2.1.2*(b)*) evaluated the association between employment in the pulp and paper industry in Norway and the risk for ovarian cancer. In addition to the assessment of occupational exposure, information was collected on hygienic use of talc and potential confounders for a subset of the cases and controls during a personal interview conducted at the mills or by telephone. Exposure to hygienic talc products was categorized as ever/never for personal use on diapers,

sanitary napkins, underwear or husband's use in the genital area. Thirty-five cases and 102 of the eligible controls or their next of kin agreed to an interview and an additional 19 women who were not cases were interviewed and included in secondary analyses as supplementary controls. A family member completed the interview (due to the death of the case or control) for 25 of the cases and 31 of the controls. Use of talc on the genital area was reported by 12 cases and 53 controls to yield an odds ratio of 1.2 (95% CI, 0.4– 3.2). [The primary limitations of this analysis were the small number of cases, the small percentage of cases and controls who were interviewed to obtain information on the covariates of interest and use of surrogate respondents to obtain information on covariates for the deceased cases and controls. The Working Group noted that hygienic exposure to talc was assessed retrospectively in the nested case–control study.]

Mills *et al.* (2004) evaluated the association between perineal exposure to talc and the risk for ovarian cancer in an ethnically diverse population from 22 counties of central California, USA. The study included 256 incident cases diagnosed between 1 January 2000 and 31 December 2001 and identified through two regional cancer registries using rapid case ascertainment procedures and 1122 controls identified by random-digit dialling. Controls were frequency-matched to the cases by age and ethnicity. Pathology reports were reviewed centrally for a subset of the cases to confirm the diagnosis, subtype and invasiveness of each cancer. Potential controls were ineligible for inclusion in the study if they were under 18 years of age, were not a resident of the counties of interest or if they had a history of epithelial ovarian cancer or bilateral oophorectomy. Among 652 cases identified during the study period, 263 (40.3%) were excluded due to: language or hearing difficulties ($n = 17$), death ($n = 76$), physician refusal ($n = 10$), severe illness ($n = 41$) or unavailability of current contact information ($n = 119$). Of the 389 eligible cases who were contacted regarding participation in the study, 256 (65.8%) agreed to participate and were interviewed. Of a total of 2327 potential controls, 740 (31.8%) were excluded from the study due to: age ($n = 80$), location of residence ($n = 21$), language difficulties ($n = 10$), previous bilateral oophorectomy ($n = 252$), severe illness ($n = 19$) or change of address or telephone number or inability to contact the woman after repeated attempts ($n = 358$). Of the 1587 potential controls who were contacted and found to be eligible, 1122 (70.7%) agreed to participate and were interviewed. All cases and controls were interviewed by telephone to obtain information on their medical history, covariates of interest and history of perineal exposure to talc, including the frequency, duration and calendar years of use. Information on talc use was unavailable for seven cases and 17 controls; thus, the final study population for this analysis included 249 cases and 1105 controls. For the final models, unconditional logistic regression adjusted for age, race/ethnicity, duration of oral contraceptive use and breastfeeding was used. Additional covariates considered to be potential confounders included family history of breast cancer or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation and duration of postmenopausal use of hormones. A history of perineal talc use was reported by 42.6% of the cases and 37.1% of the controls to yield an adjusted odds ratio of 1.4 (95% CI, 1.0–1.9). A significant trend ($P = 0.015$) with increasing frequency

of talc use was observed. The greatest risk for ovarian cancer was observed among women with the highest frequency of use (odds ratio, 1.7 for use 4–7 times per week; 95% CI, 1.1–2.6). There was a borderline significant trend with increasing duration of use ($P = 0.045$). The highest risk was observed among women with 4–12 years of use (odds ratio, 1.9; 95% CI, 1.2–3.0) and elevated but non-significant risks were seen among women with longer durations of use with odds ratios of 1.5 (95% CI, 0.9–2.3) and 1.2 (95% CI, 0.7–2.1) for 13–30 and > 30 years of use, respectively. A borderline significant trend was noted for cumulative talc use (frequency times duration of use), although this was also not clear-cut ($P = 0.051$). The highest risks were observed in the second and third quartiles of cumulative talc use. When examined according to the time of use, the risk was higher among women who had first used talc after 1975 (odds ratio, 1.9; 95% CI, 1.3–2.9) than among those who had first used talc before or during 1975 (odds ratio, 1.2; 95% CI, 0.8–1.8). Risk was also higher among women who were aged 20 years or more at first talc use than among those who were under 20 years of age and among women who initiated talc use after their first birth than among those who had some use before their first birth. When time since last use was examined, women who had last used talc 1–2 years previously had the highest risk (odds ratio, 2.4; 95% CI, 1.4–4.1); women who had last used it 3–20 years previously had an elevated but non-significant risk for ovarian cancer (odds ratio, 1.6; 95% CI, 0.9–2.7). Modification of the association between perineal use of talc and risk for ovarian cancer by tubal ligation, hysterectomy, parity, oral contraceptive use, postmenopausal use of hormones and body mass index was also evaluated. Risk was higher among women who had not had tubal ligation (odds ratio, 1.5; 95% CI, 1.1–2.2) than among those who had (odds ratio, 0.9; 95% CI, 0.5–1.7), although the interaction was not statistically significant. Risk was also higher among women who had ever been pregnant (odds ratio, 1.4; 95% CI, 1.1–2.0) than among those who had never been pregnant (odds ratio, 0.9; 95% CI, 0.4–2.3) and among women who had no history of oral contraceptive use (odds ratio, 1.6; 95% CI, 1.0–2.6) than among those who had used oral contraceptives (odds ratio, 1.3; 95% CI, 0.9–1.8). No evidence was found of a modification of effect by hysterectomy status, body mass index or postmenopausal use of hormones. [Limitations of this study included the low participation rate and relatively small number of cases. In addition, pathology was not confirmed for all cases, which may have resulted in some misclassification of histological subtype.]

2.3   Use of talc in pleurodesis

The use of talc or iodized talc to produce pleurodesis began in the 1930s as a treatment for recurrent spontaneous pneumothorax or pleural effusions. The therapy involves the introduction of 0.5–10 g talc directly into the pleura using intrapleural injection. In recent decades, the therapy has most commonly been restricted to use for the treatment of malignant pleural effusions.

An individual case report described a lung adenocarcinoma that was diagnosed 2 years after pleurodesis with iodized talc (Jackson & Bennett, 1973).

A survey was reported (Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979) of the long-term effects of pleurodesis with talc and kaolin among a series of British patients who were followed for 14–40 years. The one talc mentioned (BP Indian Finex) was reported not to contain fibrous amphiboles, but it was unclear if that was true of all the talcs used. Three lung cancers were observed (2.14 expected, $P > 0.3$) among 210 talc pleurodesis patients. Two of the lung cancer patients developed tumours on the opposite side from where treatment had occurred (18-month and 19-year intervals between treatment and death). The third patient had an oat cell carcinoma (site unknown) and died 32 years after treatment. No cases of mesothelioma were reported.

Viskum *et al.* (1989) reported on 99 Danish patients who had been treated in 1954–64 by pleurodesis with talc at doses that ranged from 0.5 to 4.9 g and who were followed for at least 20 years. Three deaths from lung cancer occurred [expected number of cases not provided], one on the side opposite from where treatment had occurred and two with no origin reported. No cases of mesothelioma were reported. [The Working Group noted that these reports are difficult to interpret because of the high prevalence of lung disease in the patient groups, which could be related to risk factors such as tobacco smoking. The type or source of talc used was not clear, although it was assumed to be pharmaceutical grade. No case of mesothelioma was observed but the number of expected cases would probably be very low.]

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TALC   381

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382   IARC MONOGRAPHS VOLUME 93

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3. Studies of Cancer in Experimental Animals

The Working Group identified an issue that relates to the interpretation of several of the inhalation and intratracheal instillation studies of talc. A lesion that is frequently seen in rats that have been exposed by inhalation to a range of poorly soluble particles such as talc has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell tumour'. Various authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al*., 1993; Carlton, 1994; Mauderly *et al*., 1994; Boorman & Seely, 1995; Rittinghausen *et al*., 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain.

The Working Group noted that, in many of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, that there was a lack of information on fibre content or particle size.

3.1   Oral administration

Rat

Groups of 25 male and 25 female Wistar rats, 10 weeks of age, received about 50 mg/kg body weight (bw) per day of commercial talc [characteristics unspecified] in the diet (average survival, 649 days) or standard di*et al*one for life (average survival, 702 days). No significant difference in tumour incidence was found in the treated animals compared with control animals (Gibel *et al*., 1976).

Groups of 16 male and 16 female Wistar-derived rats, 21–26 weeks of age, were fed 100 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) per day per rat in the diet for 5 months (talc-containing diet was actually given for 101 days) and were then maintained on basal diet for life (average survival, 614 days). No differences in tumour incidence were noted between treated animals and eight male and eight female control animals fed basal diet throughout (average survival, 641 days) (Wagner *et al*., 1977). [The Working Group noted the limited exposure period and the advanced age of the animals at the start of the study.]

3.2   Inhalation exposure

3.2.1   *Mouse*

Groups of 47–49 male and 48–50 female B6C3F$_1$ mice, 7 weeks of age, that were fed an NIH-07 diet, were exposed by inhalation to aerosols containing 0, 6 or 18 mg/m^3 MP 10–52 grade talc for 6 hours per day on 5 days per week for up to 104 weeks (dose equivalent, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). MP 10–52 grade is a high-purity microtalc (from a strip mine located in Missouri State, USA) that has a maximal particle size of 10 µm and is reported to contain no tremolite or any asbestiform minerals. After analysis, the talc was found to be free of asbestos and almost free of silica. The average mass mean aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the talc aerosols were calculated to be 3.3 ± 1.9 µm and 3.6 ± 2.0 µm for the 6- and 18-mg/m^3 chambers, respectively. At approximately week 70, difficulties were experienced in generating the talc aerosol, and the chamber concentrations were substantially lower than the target concentrations over a period of 12 weeks. Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls, and no clinical findings were attributed to exposure to talc. No significant increases in the incidence of neoplasms were observed. The incidence of pulmonary neoplasms (males: 27%, 11% and 23%; females: 11%, 12% and 6%) was similar between exposed and control groups of mice. [The Working Group noted that the incidence of alveolar/bronchiolar adenoma or carcinoma combined in historical control B6C3F$_1$ mice fed an NIH-07 diet in National Toxicology Program inhalation studies was 26.8% for males and 10.1% for females] (National Toxicology Program, 1993).

3.2.2   *Rat*

Two groups of 12 male and 12 female Wistar-derived rats, 6–8 weeks of age, were exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m^3 Italian talc (grade 0000; ready milled; mean particle size, 25 µm in diameter; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) for 7.5 hours per day on 5 days a week for 6 or 12 months (cumulative exposures, 8200 and 16 400 mg/m$^3 \times$ h, respectively). Ten days after the end of each exposure period, six rats per group were killed; 12 rats per group died and two rats per group were unaccounted for; the remaining four rats per group were killed 1 year after the end of the exposure period. No differences were noted in the incidence of lung tumours compared with 24 male and 24 female untreated controls (Wagner *et al*., 1977). [The Working Group noted the limited number of animals allowed to survive longer than 12 months after the end of each exposure period.]

Groups of 49 or 50 male and 50 female Fischer 344/N rats, 6–7 weeks of age, were exposed by inhalation to aerosols of 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for 6 hours per day on 5 days per week until mortality in any exposure group

reached 80% (113 weeks for males and 122 weeks for females; dose equivalent, 0, 2.8 or 8.4 mg/kg bw per day for males GSD and 0, 3.2 or 9.6 mg/kg bw per day for females). The average MMAD and the GSD of the talc aerosols were calculated to be 2.7 ± 1.9 μm and 3.2 ± 1.9 μm for the 6- and 18-mg/m^3 chambers, respectively. At week 11, the chamber concentration for the 18-mg/m^3 group varied from approximately 30 to 40 mg/m^3 for a period of 7 weeks because of difficulties with the systems used to monitor aerosol concentration. In addition, at approximately week 70, difficulties were experienced in generating the talc aerosol for a period of 12 weeks during which the chamber concentrations were substantially lower than the target concentrations. The survival of treated male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the lifetime study. Exposure to talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. The authors considered that the squamous cysts represented a form of squamous metaplasia. The incidence of alveolar/bronchiolar adenoma and carcinoma (combined) in female rats was: control, 1/50 (carcinoma, 0/50); low-dose, 0/48; high-dose, 13/50 (carcinoma, 5/50) and was significantly greater ($P < 0.001$) in the high-dose group than in controls (carcinoma, $P = 0.028$). The incidence of pulmonary neoplasms in exposed male rats was similar to that in controls. Adrenal medulla pheochromocytomas (benign and malignant combined) occurred with a significantly positive trend in males (control, 26/49; low-dose, 32/48; high-dose, 37/47; $P = 0.007$) and females (control, 13/48; low-dose, 14/47; high-dose, 23/49; $P = 0.014$), and the incidence in the high-dose groups was significantly greater than that in controls ($P = 0.006$ for males, $P = 0.024$ for females). The incidence of malignant pheochromocytomas in females was: control, 0/48; low-dose, 1/47; high-dose, 10/49 ($P = 0.001$). Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females, the incidence of hyperplasia in exposed males was significantly lower than that in controls (National Toxicology Program, 1993). [The Working Group noted that some authors have indicated that stress and hypoxia may lead to a proliferation of chromaffin cells and eventually to pheochromocytomas. An increase in the incidence of these tumours was also observed in several other National Toxicology Program studies that used particulates and the same rat strain in which the background incidence of this type of tumour was quite high (Ozaki *et al*., 2002; Melnick *et al*., 2003). The Working Group also noted that this type of tumour was not reported in particle inhalation studies other than those of the National Toxicology Program, and hence felt that this increase may not be related to talc.]

386   IARC MONOGRAPHS VOLUME 93

3.2.3   *Hamster*

In a lifetime experiment, three groups of 50 male and 50 female Syrian golden hamsters, 4 weeks of age, were exposed by inhalation to an aerosol of talc baby powder that was prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile) for 3, 30 or 150 minute per day on 5 days a week for 30 days. The mean aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and a MMAD of 4.9 μm. A sham-exposed group comprised 25 males and 25 females. Two further groups of hamsters, 7 weeks of age, were exposed to talc aerosol for 30 or 150 minute per day for 300 days. The mean aerosol concentration was 27.4 mg/m^3, with a measurable respiratory fraction of 8.1 mg/m^3 and a MMAD of 6.0 μm. Another sham-exposed group comprised 25 males and 25 females. The survivors of the last two talc-exposed groups were killed at the age of 20 months. At that time, 20% of the males were still alive and all females were dead. No primary tumours were observed in the lungs in any of the hamsters, although the incidence of alveolar-cell hyperplasia in the groups given talc aerosol for 30 or 150 minutes per day for 300 days was 25% compared with 10% in the control group (Wehner *et al*., 1977, 1979). [The Working Group noted the short daily exposure time and the high mortality rate.]

3.3   Intratracheal administration

Hamster

Four groups of 24 male and 24 female Syrian golden hamsters, 9 weeks of age, received 18 weekly intratracheal instillations of 3 mg talc (USP grade; silica oxide, 61–63%; magnesium oxide, 32–34%; other dusts, 0.85–1.06%; 93.3% < 25 μm in diameter) in 0.2 mL saline with or without 3 mg benzo[*a*]pyrene, or 0.2 mL saline alone or were untreated. The animals were allowed to live out their lifespan (average 50% survival, 46–55 weeks). No respiratory tract tumours were observed in the talc-treated, saline-treated or untreated groups. Malignancies were observed in 33/45 animals treated with talc plus benzo[*a*]pyrene (Stenbäck & Rowlands, 1978). [The Working Group noted the short survival of the animals.]

3.4   Subcutaneous administration

Mouse

Fifty female R3 mice, 3–6 months of age, were given single subcutaneous injections of 0.2 mL of a mixture of 8 g talc [type unspecified] and 20 g peanut oil (delivered dose, about 80 mg) and were observed for life (average 50% survival, 596 days). No local tumour was observed (Neukomm & de Trey, 1961).

TALC   387

In a study reported in an abstract, female Marsh mice, 3 months of age, received single subcutaneous injections of 20 mg USP talc and were observed for 18–21 months. No tumour developed at the injection site in 26 treated animals or in 24 saline-injected controls (Bischoff & Bryson, 1976).

3.5   Intraperitoneal administration

3.5.1   *Mouse*

In a study that investigated the response to intraperitoneally injected asbestos, control groups of 12, four, five, six, five and 12 white male mice [age unspecified] were injected intraperitoneally with a 0.5-mL suspension (50%) of talc in saline and killed 26, 57, 112, 147, 170 and 343 days after injection, respectively. Talc was described as 6505–147–0000 Talc, USP V (no further analysis was made). Histopathological examination was performed, and no mesotheliomas or other neoplasms were reported (Jagatic *et al*., 1967).

In a study reported as an abstract, female Marsh mice, 3 months of age, received a single intraperitoneal injection of 20 mg USP talc and were observed for 18–21 months. Intraperitoneal lymphoid tumours occurred in 5/22 treated animals and in 6/28 saline-treated controls (Bischoff & Bryson, 1976).

Fourty Swiss albino mice [sex unspecified], 6 weeks of age, received a single intraperitoneal injection of 20 mg ground commercial talc [type unspecified] in 1 mL saline. Within 6 months, 16 animals had died. In the 24 survivors allowed to live out their normal lifespan, three peritoneal mesotheliomas were observed, compared with 3/46 saline-treated controls (Özesmi *et al*., 1985). [The Working Group noted the occurrence of mesotheliomas in saline-treated animals.]

3.5.2   *Rat*

A group of 40 female Wistar rats, 8–12 weeks of age, received four intraperitoneal injections of 25 mg granular talc [characteristics unspecified] in 2 mL saline at weekly intervals. A group of 80 female rats was injected with 2 mL saline alone and served as controls. The rats were observed until spontaneous death or when killed in moribund state. A mesothelioma was observed in 1/36 talc-exposed rats after 587 days compared with none in 72 controls (Pott *et al*., 1974, 1976a,b).

In a study reported as an abstract, female Evans rats, 3 months of age, received a single intraperitoneal injection of 100 mg USP talc and were observed for 18–21 months. Of the treated rats, 3/27 developed tumours (one lymphosarcoma and one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) compared with none of 26 saline-treated controls (Bischoff & Bryson, 1976).

3.6   Intrapleural and intrathoracic administration

3.6.1   *Mouse*

In a study reported as an abstract, male Marsh mice, 3 months of age, received a single intrathoracic injection of 10 mg USP talc. After 18–21 months, 5/47 treated mice had tumours (two adenocarcinomas and three lymphoid tumours of the lung) compared with none of 48 saline-injected controls (Bischoff & Bryson, 1976).

3.6.2   *Rat*

In a study reported as an abstract, female Evans rats, 3 months of age, received single intrathoracic injections of 50 mg USP talc. After 18–21 months, intrathoracic reticulum-cell sarcomas or lymphomas were observed in 7/30 talc-treated rats, 8/32 saline-treated rats and 7/28 untreated controls (Bischoff & Bryson, 1976).

In a lifetime study, a group of 24 male and 24 female Wistar-derived rats, 8–14 weeks of age, received a single intrapleural injections of 20 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) in 0.4 mL saline. The mean survival time of the treated rats (655 days) was similar to that of 24 male and 24 female controls (691 days) that were injected with saline. No mesothelioma was detected in either group; one small pulmonary adenoma was found in one treated rat that died 25 months after injection (Wagner *et al*., 1977).

Following thoracotomy, groups of 30–50 female Osborne-Mendel rats, 12–20 weeks of age, received intrapleural implantations of 40 mg of one of seven grades of refined commercial talc from separate sources in hardened gelatin. The rats were followed for 2 years, at which time survivors were killed. The incidence of pleural sarcomas was: talc 1, 1/26; talc 2, 1/30; talc 3, 1/29; talc 4, 1/29; talc 5, 0/30; talc 6, 0/30; talc 7, 0/29; untreated controls, 3/488 (0.6%); and controls that received implants of 'non-fibrous' materials described by the authors as 'non-carcinogenic', 17/598 (3%) (Stanton *et al*., 1981).

3.7   Ovary implantation

Rat

In a study that investigated the effect of implanted talc on the rat ovary, a group of 10 female Sprague-Dawley rats, 10–15 weeks of age, received implants of 100 µL of a talc suspension in saline (100 mg/mL) onto the surface of the ovary by intrabursal injection. The talc was described as Italian 00000 (particle size, 0.3–14 µm) and contained no asbestos. Three sham-operated and three sham-treated control animals were included. Animals were killed after 12 months and histopathological examination of the ovaries was performed. Small focal areas of papillary change that were considered to be

preneoplastic changes were seen in the surface epithelium of 4/10 treated animals (0/6 controls). No neoplasms were reported (Hamilton *et al*., 1984). [The Working Group noted that groups of animals implanted for 1, 3, 6 or 18 months were also included, but no results were reported for any of these groups.].

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4. Mechanistic and Other Relevant Data

The general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discusssed in the Monograph on carbon black in this volume.

4.1   Humans

4.1.1   *Deposition, retention and clearance*

Talc particles have been found at autopsy in the lungs of patients with 'talc pneumoconiosis' (Schepers & Durkan, 1955a; Seeler, 1959; Kleinfeld *et al.*, 1963; Abraham & Brambilla, 1980; Berner *et al.*, 1981; Vallyathan & Craighead, 1981). Talc, in the form of platy or elongated particles, has been found at autopsy in the lungs of urban residents, farmers and asbestos miners (Seeler, 1959; Langer *et al.*, 1971; Pooley, 1976; Gylseth *et al.*, 1984). Talc has been reported to be concentrated in lung scar tissue (Yao *et al.*, 1984). Clinically, intrapleural instillation of talc is used to induce pleural adhesions in cases of pleural effusion and pneumothorax (Rodriguez-Panadero & Antony, 1997).

Churg and Wiggs (1985) used transmission electron microscopy and energy dispersive X-ray spectroscopy to analyse the total fibrous and non-fibrous mineral content of the lungs of a group of 14 male smokers who had lung cancer but no history of occupational exposure to dust. A group of 14 control men were matched by age, smoking history and general occupational class. The average concentrations of mineral fibres and non-fibrous particles were nearly fourfold and approximately twofold higher, respectively, in the group with cancer than in the controls. Kaolinite, talc, mica, feldspars and crystalline silica comprised the majority of fibrous and non-fibrous particles in both groups.

In a subsequent study, Churg and Wiggs (1987) examined the distribution of mineral fibres in the lungs of 10 male smokers who did not have lung cancer or a history of occupational exposure to dust. The subjects were all over 50 years of age at death and had a smoking history that ranged from 15 to 100 pack–years (mean, 45±24 pack–years). The primary minerals identified were kaolinite, silica and mica and accounted for 64% of the fibres; feldspars and talc accounted for 9 and 7%, respectively. There was a significant correlation between smoking history and particle concentration (number of particles per gram of tissue) in the upper lobes. The diameters (mean±standard deviation [SD]) of talc particles in the upper and lower lobes were 1.2±0.9 μm and 0.9±1.0 μm, respectively.

Dumortier *et al.* (1989) used analytical electron microscopy to examine non-fibrous particle content in the bronchoalveolar lavage fluid of 51 occupationally

exposed subjects, six of whom were talc millers. In the latter group, two workers had almost exclusively talc in their lavage fluid, while the others had about 60% talc and 40% chlorite. In other workers, talc generally accounted for <3% of the particles in lavage fluid. It was noted that, although the exposure of one of the millers had ceased 21 years before the examination, talc particles were still present in his lavage fluid.

Talc particles have been found in stomach tumours from Japanese men (Henderson *et al.*, 1975), possibly due to ingestion of talc-treated rice (Merliss, 1971a,b). Talc particles, but apparently no other insoluble particles, were found in the subserosal stroma of hernia sacs, possibly due to ingestion of medications in which talc is present as a filler (Pratt *et al.*, 1985). Anani *et al.* (1987) reported the presence of talc fibres in the intestinal wall of a 46-year-old patient who had severe intestinal pain and was diagnosed with intestinal talcosis. A possible source of exposure was the talc contained in oral medications against tuberculosis, which the patient had taken nearly 20 years earlier over a period of 22 months (total intake of talc, 183 g).

Talc is often present as a filler in some materials used by drug addicts, which results in wide dissemination of talc particles to the lungs (Groth *et al.*, 1972; Lamb & Roberts, 1972; Farber *et al.*, 1981; Crouch & Churg, 1983), spleen, kidney, liver, brain, heart, adrenal and thyroid glands (Groth *et al.*, 1972) and even the retina (AtLee, 1972). In the lungs, most of the talc particles are found within the vessels of the alveolar walls, and are almost invariably associated with marked foreign-body granulomas (Crouch & Churg, 1983). The talc particles found in the lungs are larger after intravenous injection than after inhalation (Abraham & Brambilla, 1980) (see Section 4.1.2 for a discussion of the associated toxic effects).

In view of epidemiological evidence of a possible association between talc use for perineal hygiene and an increased risk for ovarian cancer (see Section 2), several studies have been conducted in women to determine potential retrograde movement of particles through the reproductive tract to the ovaries. These studies involved women who were about to undergo gynaecological surgery, mostly for diseases or complications of the reproductive tract and organs. Therefore, broad interpretations with regard to healthy women may be limited.

Egli and Newton (1961) found that inert carbon particles deposited in the vagina in two of three patients travelled to the fallopian tubes in about 30 minutes. De Boer (1972) concluded that Indian ink deposited below the level of the cervix is unlikely to travel quickly through the reproductive tract. In contrast, the findings of Venter and Iturralde (1979) and Mostafa *et al.* (1985) suggested that retrograde transport to the fallopian tubes is possible. Henderson *et al.* (1971) reported the actual presence of talc in histological specimens from 10 of 13 ovarian tumours, 12 of 21 cervical tumours and five of 12 normal ovarian tissues. Subsequently, Henderson *et al.* (1979) and Heller *et al.* (1996) provided further evidence of the presence of talc in the ovaries of women who had purportedly had perineal exposure to talc. However, in the latter study, no relation was found between talc-particle counts and reported perineal use of talc.

4.1.2 *Toxic effects*

The toxic effects of talc in humans are dependent on the route and dose of administration and the physicochemical properties of the talc. In addition, talc products commonly contain other potentially toxic minerals (see Section 1).

Talc pneumoconiosis is somewhat more prevalent and severe among people who are exposed to talc that contains asbestiform minerals than among those who are exposed to talc with no such impurities (Kleinfeld *et al.*, 1963). The form of this pneumoconiosis varies widely, from a simple asymptomatic type (Vallyathan & Craighead, 1981) to disabling conglomerate pneumoconiosis (Hunt, 1956; Graham & Gaensler, 1965; Miller *et al.*, 1971). Mixed-dust pneumoconiosis is frequently seen, including silicosis, asbestosis and occasionally other forms (Kleinfeld *et al.*, 1963; Mark *et al.*, 1979).

Several early reports described 'talcum powder granuloma' that arose from the use of talc on surgical gloves (reviewed in Eiseman *et al.*, 1947). Subsequent reports of cases have documented a variety of surgical complications, including adhesions, pseudotumours and sinus tracts that were attributable to exposure to talc (Lichtman *et al.*, 1946; Eiseman *et al.*, 1947; reviewed by Hollinger, 1990). Both skin granulomas and talc pneumoconiosis have been reported after liberal use of talc on the body (Tye *et al.*, 1966; Nam & Gracey, 1972; Wells *et al.*, 1979; Tukiainen *et al.*, 1984; Wehner, 1994).

Respiratory distress syndrome, which can be fatal, has been described in children following massive accidental inhalation of talcum powder (Cless & Anger, 1954; Molnar *et al.*, 1962; Lund & Feldt-Rasmussen, 1969; Gould & Barnardo, 1972) and in adult patients after talc pleurodesis (Rehse *et al.*, 1999).

A variety of pathological effects arise from the intravenous use by drug addicts of products that contain talc. These include micronuclear pulmonary opacities (Hopkins & Taylor, 1970; Arnett *et al.*, 1976; Waller *et al.*, 1980), angiothrombotic pulmonary hypertension (Wendt *et al.*, 1964; Paré *et al.*, 1979; Waller *et al.*, 1980) and conglomerate pulmonary lesions (Sieniewicz & Nidecker, 1980; Crouch & Churg, 1983). In addition, retinopathy, cerebral microembolization and granulomas of the liver, lymph nodes and kidneys have been reported (Min *et al.*, 1974; Paré *et al.*, 1979; Carman, 1985).

A series of cross-sectional studies reported from the New York State Department of Labour (Kleinfeld *et al.*, 1955, 1963, 1964, 1973) have documented talc pneumoconiosis in talc miners and millers, especially among tremolitic talc workers. The cases were associated with pleural plaques, restrictive or obstructive breathing disorders and decreased vital capacity of the lungs. The prevalence of disease was lower among those with lower cumulative exposure to dust and among those who processed granular rather than fibrous talc.

A series of cross-sectional studies that described talc pneumoconiosis in workers in talc mining, milling and manufacture in Italy (Rubino *et al.*, 1963; Tronzano *et al.*, 1965) found that the prevalence was related to extent and duration of exposure and that talcs contaminated with tremolite, serpentine and quartz were associated with significant pneumoconiosis.

One representative, well-controlled study among 80 workers exposed in the rubber industry to Vermont talc, which is reported to have a low content of silica and fibres, showed significantly increased respiratory symptoms, impaired ventilatory function and increased respiratory morbidity, but no radiographic abnormality (Fine *et al*., 1976).

There has been some concern that talc may cause adult respiratory distress syndrome when instilled into the pleural space for pleurodesis (Rinaldo *et al.*, 1983; Bouchama *et al.*, 1984; Kennedy *et al.*, 1994; Rehse *et al.*, 1999; Light, 2000). Relatively recent cases were observed when talc was both insufflated and used as a slurry (Brant & Eaton, 2001; Scalzetti, 2001). However, other case series did not report the development of this disease (Weissberg & Ben-Zeev, 1993; Rodriguez-Panadero & Antony, 1997; Sahn, 2000; Ferrer *et al.*, 2001, 2002; Cardillo *et al.*, 2006). Many of the patients in the case reports had co-morbid conditions. [The Working Group noted that the talc used in these reports was not always characterized mineralogically and may have contained contaminants.]

The role of exposure to talc in the development of ovarian cancer has raised concerns (see Section 2). The normal ovarian epithelium is known to express several mucins that are protective against epithelial inflammation and injury (Lalani *et al.*, 1991; Gipson *et al.*, 1997; Ness & Cottreau, 1999; Taylor-Papadimitriou *et al.*, 1999; Ness *et al.*, 2000; La Vecchia, 2001). Several epithelial cancers, such as breast and ovarian cancer, express mucin (MUC-1) which is upregulated and aberrantly glycosylated in many carcinomas (Taylor-Papadimitriou *et al.*, 1999).

Cramer *et al.* (2005) examined the association between the characteristics of women with no previous diagnosis of ovarian cancer and levels of antibodies to MUC-1, a protein that is expressed by normal epithelial cells and overexpressed by ovarian cancer cells. The study participants were 705 controls from a case–control study of ovarian cancer conducted in Massachusetts and New Hampshire (USA) between 1998 and 2003. Plasma specimens collected from participants at enrolment into the study were analysed for anti-MUC-1 antibody levels using an enzyme-linked immunosorbent assay. Forty-eight cases of ovarian cancer with pre-operative blood specimens were also included in additional analyses; further 668 cases of ovarian cancer were included in the analyses to evaluate risk factors for ovarian cancer. Multivariable logistic regression, Spearman rank correlations and generalized linear models were used in the statistical analyses to determine which characteristics were associated with anti-MUC-1 antibody production and which were associated with the risk for ovarian cancer. Women who reported no previous genital use of talc were more likely to have antibodies to MUC-1 than women who had a history of regular genital exposure to talc (38.1% versus 28.6%; $P = 0.04$). In addition, there was a borderline significant trend between frequency of talc use and lower anti-MUC-1 antibody levels ($P = 0.11$), after adjustment for other characteristics that affect antibody levels. Several conditions associated with increased antibody production were associated with a decreased risk for ovarian cancer. The authors concluded that these findings suggest that the presence of anti-MUC1 antibodies is inversely correlated with risk for ovarian cancer. [Limitations of this study included the potential for bias in the participants' recollection of their genital use of talc, due to the case–control study design.

In addition, antibody levels in the cases and controls may not be comparable, since the presence of a cancer may affect anti-MUC-1 antibody levels.]

4.2   Experimental systems

4.2.1   *Deposition, retention and clearance*

The deposition, translocation and clearance of talc was investigated in 44 female golden Syrian hamsters (10 weeks of age) that were exposed by nose-only inhalation for 2 hours to 40–75 mg/m^3 neutron-activated talc (Johnsons's Baby Powder®, lot 228p; median aerodynamic diameter, 6.4–6.9 µm). The powder was high-grade cosmetic talc and consisted of 95% (w/w) platy talc mineral (Wehner *et al.*, 1977a). Alveolar deposition was approximately 20–80 µg, which represented 6–8% of the inhaled amount. The retention half-time of the talc deposited in the alveoli was 7–10 days, and alveolar clearance was reported to be essentially complete 4 months after exposure. No translocation of talc to liver, kidneys, ovaries or other parts of the body was found (Wehner *et al.*, 1977b). [The Working Group noted that the unusually short clearance time may be related to limitations in the sensitivity of the detection methods and the large size of the particles used.]

In rats exposed for 7.5 h per day on 5 days a week to aerosols of Italian talc (mean concentration of respirable dust [not further defined], 10.8 mg/m^3), the mean amounts of talc retained in the lung were 2.5, 4.7 and 12.2 mg per animal following exposures for 3, 6 and 12 months, respectively. These levels were approximately proportional to the cumulative exposures (Wagner *et al.*, 1977). In rats exposed for 6 hours per day on 5 days a week for 4 weeks to 2.3, 4.3 and 17 mg/m^3 respirable talc, the amounts retained in the lung at the end of exposure were 77, 187 and 806 µg talc/g lung, respectively (Hanson *et al.*, 1985).

Lung burdens of talc were determined in groups of 10 male and 10 female Fischer 344 rats and B6C3F$_1$ mice following exposure to asbestos-free talc for 6 hours per day on 5 days a week for 4 weeks. In rats exposed to 0, 2.3, 4.3 and 17 mg/m^3, average lung burdens were 0, 0.07, 0.17 and 0.72 mg talc/g lung, respectively. In mice exposed to 0, 2.2, 5.7 and 20.4 mg/m^3, average lung burdens of 0, 0.10, 0.29 and 1.0 mg talc/g lung, respectively, were observed. When normalized to the exposure concentration, the lung burden in mice was greater than that in rats and the normalized burden in rats increased with increasing exposure concentration (Pickrell *et al.*, 1989).

Conflicting data exist on systemic distribution following intrapleural instillation of talc (i.e. talc pleurodesis) in rats. Following administration of 10 or 20 mg talc [particle size unspecified] to rats (20 per group), talc was identified in the chest wall, lungs, heart, brain, spleen and kidneys. The authors concluded that talc is rapidly absorbed through the pleura and reaches the systemic circulation and organs 24 hours after administration (Werebe *et al.*, 1999). However, following instillation of 40 mg talc (median particle size, 31 µm) into 33 rats randomly assigned to autopsy 24 or 72 hours later, talc particles were

observed in only a few extrapulmonary organs, i.e. the brain, spleen and liver, but not the kidneys (Fraticelli *et al.*, 2002).

The systemic distribution of talc was investigated in rabbits following talc pleurodesis in two studies. In one study (Ferrer *et al.*, 2002), 10 rabbits received 200 mg/kg bw 8.4-μm asbestos-free talc particles and 10 received 200 mg/kg bw 12-μm talc particles. Five animals from each group were killed after 24 hours and five at 7 days after instillation. A tendency was seen for increased extrapulmonary distribution of the smaller particles, which were identified in the pericardium of 0/5 and 3/5 rabbits at 24 hours and 7 days, respectively. For the larger particles, one of five animals had talc in the pericardium at each time-point. Particles were identified in the liver of three of five animals exposed to the smaller particles 7 days after instillation; other groups had no particles in the liver. Small particles were found in the kidney of only 1/5 animals 24 hours after instillation. Both particle types were found in the spleen of 1/5 animals 24 hours after instillation. The results indicate that talc reached the lung parenchyma by breaking the mesothelial and elastic layer and that mobility was greater for the smaller particles.

In the other study, Montes *et al.* (2003) performed talc pleurodesis in rabbits (20 per group) at doses of 50 and 200 mg/kg bw of the small-particle talc used in the study by Ferrer *et al.* (2002). Doses were chosen to simulate treatment of a 60-kg patient with amounts of 3 and 12 g talc. The lung parenchyma of two and 14 rabbits of the low-dose and high-dose groups, respectively, contained talc. In the high-dose group, six of the animals had talc in the pericardium and five had talc in the liver; talc was not detected in these organs in the low-dose group. The results show that the systemic distribution of talc was dose-dependent.

In studies in rats, mice, guinea-pigs and hamsters that used radioactive tracer techniques, no intestinal absorption or translocation of ingested talc to the liver or kidneys was detected (Wehner *et al.*, 1977b; Phillips *et al.*, 1978). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications of talc to rabbits (Phillips *et al.*, 1978) or monkeys (Wehner *et al.*, 1985, 1986).

4.2.2   *Toxic effects*

Reviews of the literature on the biological effects of talc in experimental animals are available (Lord, 1978; Wehner, 1994).

[The Working Group noted that in most of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, information on fibre content or particle size was lacking.]

(a)   Chronic toxicity

Mild to marked arterial endothelial cell proliferation with cellular encroachment into the lumen, the occurrence of occasional foreign-body giant cells within the endothelial masses and moderate thickening of the intra-alveolar septa of the lungs were observed

after intravenous injections of talc in rabbits and guinea-pigs (Puro *et al.*, 1966; Dogra *et al.*, 1977). No effect on the rat lung was observed after intravenous injection of talc (Schepers & Durkan, 1955b) but talc granulomas were seen in rats following intrasplenic injection of talc (Eger & Canaliss, 1964).

No chronic pathological effect was associated with oral administration of Italian talc (92% pure; 100 mg per day on 101 days over 5 months) to rats (Wagner *et al.*, 1977). Intratracheal injections of talc (total dose, 150 mg) into guinea-pigs induced perivascular and peribronchiolar focal accumulations of histiocytes, fibrocytes, plasma cells and eosinophils within 1 month. After 2 years, the dominant effects were bronchiolectasia, bronchiolitis and marked fibrosis (Schepers & Durkan 1955b).

Rats exposed to dust clouds of 30–383 mg/m^3 'industrial'- or 'pharmaceutical'-grade talc for 9 months developed chronic inflammatory changes including thickening of the walls of the pulmonary arteries and, eventually, emphysema (Bethge-Iwańska, 1971).

In rats exposed by inhalation to 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 μm) for 3 months, minimal fibrosis was observed, the degree of which did not change during the observation period after exposure. Animals that were exposed for 1 year had minimal to slight fibrosis, the degree of which had increased to moderate within 1 year after cessation of exposure (Wagner *et al.,* 1977). In contrast, Syrian golden hamsters exposed to 8-mg/m^3 aerosols of cosmetic-grade talc for up to 150 minutes per day on 5 days a week for 30 days showed no histopathological change in the lungs, heart, liver, renal tissues, stomach or uterus (Wehner *et al.,* 1977c).

Two years after injection of 20 mg Italian talc (see above) into the right pleural cavity of rats, granulomas at the injection site were common, and one small pulmonary adenoma was observed, but no other relevant pathology was seen in the lungs (Wagner *et al*., 1977).

Groups of male and female rats, 6–7 weeks old, were exposed to aerosols of 0, 6 or 18 mg/m^3 talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). These exposure concentrations provided a dose equivalent of 0, 2.8 or 8.4 mg/kg bw per day for male rats and 0, 3.2 or 9.6 mg/kg bw per day for female rats. The talc used for this study was MP 10–52 Grade (see Section 3.2.1) and was found to be free from asbestos by polarized light microscopy and transmission electron microscopy. Survival of male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. No clinical findings were attributed to exposure to talc. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the study. Talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized

primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas-exchange efficiency and non-uniform intrapulmonary gas distribution (National Toxicology Program, 1993).

Groups of male and female $B6C3F_1$ mice, 7 weeks of age, were exposed by inhalation to aerosols that contained 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for up to 104 weeks (dose equivalents, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. No clinical findings were attributed to exposure to talc. Inhalation exposure to talc was associated with chronic inflammation and accumulation of macrophages in the lung. Accumulations of macrophages (histiocytes) containing talc particles were also observed in the bronchial lymph nodes (National Toxicology Program, 1993).

(b)   In-vitro toxicity

A concentration >50 μg/mL Italian talc caused a 50% reduction in the colony-forming efficiency of cultured Chinese hamster V79-4 lung cells (Chamberlain & Brown, 1978).

The concentration of talc (99% pure) required to cause 50% haemolysis of red blood cells was 6.5 mg/mL, which is more than 50-fold that of chrysotile. A concentration of 0.1 mg/mL talc caused 35% release of ^{51}Cr from Syrian hamster tracheal epithelial cells labelled with radioactive sodium chromate; the concentration was twofold that required for chrysotile (Woodworth *et al.*, 1982).

Davies *et al.* (1983) examined the effect of different types of talc on mouse peritoneal macrophages *in vitro*. Macrophages were exposed to seven specimens of high-purity talcs and the release of lactate dehydrogenase and β-glucuronidase was measured. These enzymes are produced by macrophages after they digest materials that can induce fibrosis and chronic inflammation. Enzyme release after exposure of macrophages to quartz, a known fibrogenic dust, and magnetite, a non-fibrogenic dust, was also measured. Quartz caused the greatest cytotoxic reaction *in vitro*: the amount of enzyme released increased with the dose. Magnetite had no effect. All seven talc specimens were cytotoxic to the macrophages: the levels of enzymes released were dose-related but were lower than those observed after exposure to quartz. The results show that talc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals. However, the macrophage response to talc appears to be weaker than that for other fibrogenic dusts such as quartz, and the response of macrophages to talc may be different *in vivo*.

Talc caused the release of several cytokines including C-X-C and C-C chemokines from normal human pleural mesothelial cells (Nasreen *et al.*, 1998). Pleural mesothelial cells exposed to talc did not undergo apoptosis, whereas malignant mesothelioma cell lines (ATTC CRL-2081, CRL-5820, CRL-5915) exposed to the same dose did (Nasreen *et al.*, 2000). Talc also caused the release of basic fibroblast growth factor in pleural mesothelial cells (Antony *et al.*, 2004).

In bone marrow-derived macrophages from mice, talc was found to stimulate DNA synthesis ([^{3}H]thymidine incorporation) (Hamilton *et al.*, 2001).

4.2.3   *Genetic and related effects*

Three samples of respirable talc failed to elicit significant unscheduled DNA synthesis (10, 20 and 50 µg/cm^2, 24 hours), sister chromatid exchange or aneuploidy (2, 5, 10 and 15 µg/cm^2, 48 hours) in rat pleural mesothelial cells, in contrast to various positive controls. The three samples, i.e Spanish talc (No. 5725), Italian talc (No. 5726) and French talc (No. 7841), contained 90–95% talc; the remaining contents were chlorite and dolomite. Electron microscopy analysis revealed that talc particles were taken up by the rat pleural mesothelial cells, but no aneuploidy was observed in metaphases (Endo-Capron *et al.*, 1993).

4.3   References

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400   IARC MONOGRAPHS VOLUME 93

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TALC 401

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TALC   403

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TALC   405

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5. Summary of Data Reported

5.1   Exposure data

The term 'talc' refers to both mineral talc and industrial mineral products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit (pattern) of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite and serpentine.

Mineral talc is valued for its softness, platyness, inertness and ability to absorb organic matter. It is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products. The type of talc that is currently used for cosmetic purposes in the USA does not contain detectable levels of amphibole, including asbestos. It is not known whether this is true in other countries.

Workers are exposed to talc during its mining and milling. Reported geometric mean exposure levels to respirable dust are typically in the range of $1–5$ mg/m^3. Workers may also be exposed in user industries, primarily in the rubber, pulp and paper and ceramics industries. Due to the presence of other particulates, exposure levels may be difficult to measure accurately. Consumer exposure by inhalation could occur during the use of loose powders that contain talc.

Accurate estimates of prevalence are not available. However, in some series of controls from epidemiological studies of ovarian cancer, the prevalence of use for feminine hygiene of body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries. Perineal use for such purposes seems to have been a common practice in Australia, Canada, the United Kingdom, the USA and other countries, including Pakistan. Use of cosmetic talc in the USA has declined steadily since the late 1970s.

5.2 Human carcinogenicity data

The carcinogenic effect of exposure to talc not contaminated by asbestos fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in Austria, France, Italy, Norway and the USA. The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In a case–control study nested in the combined cohorts of talc workers from Austria and France, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed. In the two studies from Italy and Norway, which included an estimate of cumulative exposure of the cohort to talc dust, the risk for lung cancer in the highest category was found to be close to or below unity. In the subgroup of miners in the study in the USA, an excess risk for lung cancer was found, which may be have been due to exposure in the workplace to radon daughters and quartz. In all the other groups of workers studied, there was no increased risk for lung cancer.

Female workers in the Norwegian pulp and paper industry had an increased risk for ovarian cancer, which, however, was attributed to exposure to asbestos. A community-based case–control study did not find an increased risk for ovarian cancer associated with occupational exposure to talc, but the prevalence of exposure was low.

Body powder containing talc has been used by women on the perineum (or genital area), on sanitary napkins and on diaphragms. In total, data from one prospective cohort study and 19 case–control studies were reviewed in the evaluation of the association of cosmetic talc use and the risk for ovarian cancer. The information collected on perineal talc use varied substantially by study (e.g. ever use versus regular use, and whether information on the mode of application, frequency or duration of use was available).

The cohort study was conducted among nurses in the USA and included 307 cases of ovarian cancer that occurred over 900 000 person–years of observation and a maximum of 14 years of follow-up. Information was collected on the frequency but not duration of regular use. Perineal use of talc was not associated with a risk for ovarian cancer.

The 20 case–control studies were conducted in Australia, Canada, China, Greece, Israel, Norway, the United Kingdom and the USA (nested case–control study), and included between 77 and 824 cases and 46 and 1367 controls. Five were hospital-based designs and the others were population-based studies. The Working Group designated a subset of these studies as being more informative based on the following characteristics: the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

Eight population-based case–control studies from Australia, Canada (Ontario) and the USA (two non-overlapping studies in Boston, MA, and one each in California, Delaware Valley, eastern Massachusetts and New Hampshire and Washington State) were thereby identified as being more informative. The selected studies included at least 188 cases and had participation rates that generally ranged from 60 to 75%. Among these eight studies, the prevalence of use of body powder among controls ranged from 16 to 52%; however,

information on exposure was not collected in a comparable manner across studies. In addition, the frequency and duration of use or total lifetime applications were investigated in several studies as well as consideration of prior tubal ligation or simple hysterectomy. Only sparse data were available on whether women had used body powder before or after the mid-1970s.

The relative risks for ovarian cancer among users of body powder (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 11 case–control studies, most also reported relative risks of this magnitude or higher. The subset of studies that assessed use of talc on a diaphragm were relatively uninformative due to their lack of precision.

Results on exposure–response relationships were presented in the cohort study and in seven of the more informative case–control studies. In the cohort study, no exposure–response trend was apparent. Positive exposure–response trends were apparent in the two Boston-based studies that presented the most comprehensive analysis. In the Canadian and Californian studies, a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case–control studies, no consistent trend was observed and the strongest associations tended to be seen among the shorter-term or less frequent talc users.

The cohort study and four of the eight more informative case–control studies presented results on histological type of ovarian cancer. When the analysis of the cohort study was restricted to the 160 serous invasive cases, a statistically significant increase in risk of about 40% was observed. The risk increased with increasing frequency of body powder use. Risks for serous ovarian cancer were somewhat greater than those for other histological types in two of the four case–control studies in which the contrast was reported. Results for other histological types were inconclusive.

The Working Group carefully weighed the various limitations and biases that could have influenced these findings. Non-differential misclassification of talc use, given the relatively crude definitions available, would have attenuated any true association. Although the available information on potential confounders varied by study, most investigators accounted for age, oral contraceptive use and parity. In most studies, only the adjusted relative risks were presented; however, in the three studies in which both age-adjusted and fully adjusted estimates were provided, relative risks did not differ materially, suggesting minimal residual confounding.

It is possible that confounding by unrecognized risk factors may have distorted the results. One or more such factors, if they are causes of ovarian cancer and also associated in the population with perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none. In order for such an unrecognized risk factor to induce the consistent pattern of excess risks in all of the case–control studies, it would be necessary for the factor to be associated with perineal talc use across different countries and different decades. While the range of countries and decades covered by the more informative case–control studies is not very broad, it provides some

diversity of social and cultural context and thereby reduces the likelihood of a hidden confounder.

There was a distinct pattern of excess risk discernible in all of the case–control studies when users were compared with non-users; however, methodological factors needed to be considered. First, while chance cannot be ruled out as an explanation, it seemed very unlikely to be responsible for the consistent pattern of excess risks. A second possible explanation would be recall bias, to which case–control studies may be particularly susceptible. This may have been the case if there had been widespread publicity about the possible association between the use of body powder and cancer. In such circumstances, it is possible that women who had ovarian cancer could be more likely than women who did not to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness..There was a flurry of publicity in the USA in the mid-1970s concerning the possible risks for cancer posed by the use of talc-based body powders. Following an industry decision to market talc powders with no asbestos, it was the opinion of the Working Group that there had not been widespread public concern about this issue, at least until very recently. Therefore, the Working Group considered it unlikely that such a bias could explain the set of consistent findings that stretch over two decades. The Working Group believed that recall bias was a possibility inherent in the case–control studies and could not be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

The Working Group searched for documentation on the presence of known hazardous minerals in talc-based body powders. There were strong indications that these products contained quartz in the mid-1970s and still do. There were also indications that occasional small concentrations of asbestos were present in these products before the mid-1970s, but the available information was sparse, sampling methods and detection limits were not described, and the range of locations where data were available was extremely limited. As a result, the Working Group found it difficult to identify a date before which talc-based body powders contained other hazardous minerals and after which they did not, or to have confidence that this would be applicable worldwide. In addition, the epidemiological studies generally do not provide information about the years during which the female subjects were exposed. Consequently, the Working Group could not identify studies in which an uncontaminated form of talc was the only one used by study subjects. Nevertheless, the Working Group noted that, even in the most recent studies in the USA, where exposure histories may have been much less affected by hazardous contaminants of talc, the risk estimates were not different from the early studies in which the possibility of such exposure was more likely.

To evaluate the evidence on whether perineal use of talc causes an increased risk for ovarian cancer, the Working Group noted the following:

• The eight more informative case–control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case–control studies examined exposure–response

relationships; two provided evidence supporting such a relationship, two provided mixed evidence and three did not support an association.

• The cohort study neither supports nor strongly refutes the evidence from the case–control studies.

• Case–control studies were susceptible to recall bias which could tend to inflate risk estimates but to an unknown degree.

• All of the studies were susceptible to other potential biases which could either increase or decrease the association.

• All of the studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

5.3   Animal carcinogenicity data

Talc of different grades was tested for carcinogenicity in mice by inhalation exposure, intrathoracic, intraperitoneal and subcutaneous injection, in rats by inhalation exposure, intrathoracic injection, intraperitoneal injection, oral administration and intrapleural and ovarian implantation, and in hamsters by inhalation exposure and intratracheal injection.

In male and female rats exposed by inhalation to a well-defined talc, the incidence of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) was significantly increased in female rats. The incidence of adrenal medulla pheochromocytomas (benign, malignant or complex (combined)) showed a significant positive trend and the incidence in high-dose males and females was significantly greater than that in controls. The incidence of malignant pheochromocytomas was also increased in high-dose females. The Working Group did not consider it probable that the increased incidence of pheochromocytomas was causally related to talc but, based on the experimental data available, neither could talc-related effects be excluded.

Tumour incidence was not increased following the intrapleural or intrathoracic administration of a single dose of various talcs to rats. In two studies of intraperitoneal administration in rats, no increase in the incidence of mesotheliomas was observed. No increased incidence of tumours was produced in rats in two studies of talc administered in the diet or in another study of the implantation of talc on to the ovary.

Tumour incidence was not increased in mice following the inhalation of talc in one study, the intrathoracic administration of a single dose of various talcs in another study or the administration of talc by intraperitoneal injections in three studies. A single subcutaneous injection of talc into mice did not produce local tumours.

Tumour incidence was not increased following inhalation or intratracheal administration of talc to hamsters.

5.4   Mechanistic considerations and other relevant data

Different mechanisms are probably operative in the effects of talc on the lung and pleura, depending on the route of exposure.

TALC   411

In humans, deposition, retention and clearance of talc have been insufficiently studied, although talc particles have been found at autopsy in the lungs of talc workers.

In humans and experimental animals, the effects of talc are dependent on the route of exposure, and the dose and properties of the talc. Talc pneumoconiosis was somewhat more prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. However, the role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Among drug users, intravenous injection of talc present as a filler in the drugs resulted in microembolization in a variety of organs and alterations in pulmonary function.

In animal studies, talc has been shown to cause granulomas and mild inflammation when inhaled. Observations of the effects that occurred in the lungs of rats exposed by inhalation to talc suggested that the operative mechanisms may be similar to those identified for carbon black, and talc is known to cause the release of cytokines, chemokines and growth factors from pleural mesothelial cells.

In humans, intrapleural administration of talc as a therapeutic procedure results in pleural inflammation which leads to pleural fibrosis and symphysis. Pleural fibrosis is the intended effect of intrapleural administration of talc in patients with malignant pleural effusions or pneumothorax. Animal studies suggested that extrapulmonary transport of talc following pleurodesis increases with decreasing particle size and increasing administered dose. Talc has been shown to cause apoptosis of malignant cells *in vitro*.

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. Several studies have been conducted in women to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These have been conducted in women who were about to undergo gynaecological surgery, most of whom had diseases or complications of the reproductive tract and organs that required surgery. The findings reported in these studies may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies. In addition, most of the studies had little or no further information on the use of talc products for perineal hygiene or changes in habits that may have preceded surgery. On balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak. In women with impaired clearance function, some evidence of retrograde transport was found. Studies in animals (rodents, langomorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.

In one study, predictors of the presence of antibodies to mucin protein were inversely related to the risk for ovarian cancer and exposure to powder containing talc.

No data were available on the genotoxic effects of exposure to talc in humans. The limited number of studies available on the genetic toxicology of talc *in vitro* gave negative results.

6. Evaluation and Rationale

6.1   Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

6.2   Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

6.3   Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*.

Inhaled talc not containing asbestos or asbestiform fibres is *not classifiable as to its carcinogenicity (Group 3)*.

6.4   Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as evidence regarding the potential mechanisms through which talc might cause cancer in humans.

The Working Group found little or inconsistent evidence of an increased risk for cancer in the studies of workers occupationally exposed to talc. The studies of talc miners and millers were considered to provide the best source of evidence, but no consistent pattern was seen. One study observed an excess risk for lung cancer among miners, but confounding from exposure to other carcinogens made it difficult to attribute this to talc and no excess risk was seen in millers. Other studies also found no increased cancer risk or no higher risk with increasing cumulative exposure. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether inhaled talc not containing asbestos or asbestiform fibres causes cancer in humans.

For perineal use of talc-based body powder, many case–control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding exposure–response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that

TALC   413

exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

In one study of rats that inhaled talc, an excess incidence of malignant lung tumours was seen in females. The same study observed an excess incidence of pheochromocytomas in the adrenal medulla in both sexes, but the Working Group was divided as to whether these rare tumours could be attributed to exposure to talc. Other studies in rats and mice using different routes of administration did not find an excess of cancer, and two studies in rats were considered to be inadequate for evaluation. Based on the one positive study, the Working Group found that there was *limited evidence* of carcinogenicity of inhaled talc in experimental animals. There was no agreement within the Working Group as to whether the evidence on pheochromocytomas should be taken into account in the evaluation of animal data.

LIST OF ABBREVIATIONS

(* in Tables only)

A4*	not classifiable as a human carcinogen
AM	arithmetic mean
ASTM	American Society for Testing and Materials
ATP	adenosine triphosphate
BAL	bronchoalveolar lavage
BaP*	benzo[*a*]pyrene
bw	body weight
2B*	possible carcinogenic to humans
3B*	substance for which in-vitro tests or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification
Ca*	carcinogen
CI	confidence interval
CIP*	capteur individuel de poussière [personal dust sampler]
CKSC	cystic keratinizing squamous-cell
CMD	count median diameter
CYP	cytochrome P450
DBPA*	dibutyl phthalate absorption
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 sec
FF*	fast-extruding furnace
FVC	forced vital capacity
GM	geometric mean
GM–CSF	granulocyte macrophage colony-stimulating factor
GPF*	general-purpose furnace
GSD	geometric standard deviation
GSH	glutathione
GST	glutathione *S*-transferase
HAF	high-abrasion furnace black
HLA	human leukocyte antigen
HPLC	high-performance liquid chromatography
Hprt	hypoxanthine(guanine)phosphoribosyl transferase

–415–

416   IARC MONOGRAPHS VOLUME 93

I*   inhalable dust
ICRP   International Commission in Radiological Protection
IFN   interferon
Ig   immunoglobulin
IL   interleukin
ILO   International Labour Organization
IOM   Institute of Occupational Medicine
K*   included in the list of substances considered
                            carcinogenic
MAK*   maximum concentration in the workplace
MAPK   mitogen-activated protein kinase
MCP   monocyte chemotactic protein
MIP   microphage inflammatory protein
MMAD   mass median aerodynamic diameter
mppcf   million particles per cubic foot
MT*   medium thermal
MUC   mucin
NA*   not available
NF   nuclear factor
N_F*   number of factories
NR*   not reported
N_S*   number of samples
NSA*   nitrogen surface area
OEL*   observed effect level
8-oxo-DG   8-oxo-7,8-2′-deoxyguanosine
PAH   polycyclic aromatic hydrocarbon
PEL*   permissible exposure limit
PM   particulate matter
pop.*   population
R*   respirable dust
REL*   recommended exposure limit
S9   metabolically activated fraction
SAF*   superabrasion furnace
SD*   standard deviation
SES*   socioeconomic status
SIR   standardized incidence ratio
SMPS   scanning mobility particle sizer
SMR   standardized mortality ratio
SRF   semi-reinforcing furnace black
STEL*   short-term exposure limit
STSA*   statistical thickness surface area
T*   total dust
T/P   coal-tar pitch

LIST OF ABBREVIATIONS   417

TI*	total inhalable
TLV*	threshold limit value
TME*	trimethylol ethane
TMP*	trimethylol propane
TNF	tumour necrosis factor
TWA	time-weighted average
UV	ultraviolet
VEGF	vascular endothelial growth factor
WL	working level

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS*

The volume, page and year of publication are given. References to corrigenda are given in parentheses.

A

Alcohol drinking	*44* (1988); *96* (2010)
Aldicarb	*53*, 93 (1991)
Aldrin	*5*, 25 (1974); *Suppl. 7*, 88 (1987)
Allyl chloride	*36*, 39 (1985); *Suppl. 7*, 56 (1987); *71*, 1231 (1999)
Allyl isothiocyanate	*36*, 55 (1985); *Suppl. 7*, 56 (1987); *73*, 37 (1999)
Allyl isovalerate	*36*, 69 (1985); *Suppl. 7*, 56 (1987); *71*, 1241 (1999)
Aluminium production	*34*, 37 (1984); *Suppl. 7*, 89 (1987); *92*, 35 (2010)
Amaranth	*8*, 41 (1975); *Suppl. 7*, 56 (1987)
5-Aminoacenaphthene	*16*, 243 (1978); *Suppl. 7*, 56 (1987)
2-Aminoanthraquinone	*27*, 191 (1982); *Suppl. 7*, 56 (1987)
para-Aminoazobenzene	*8*, 53 (1975); *Suppl. 7*, 56, 390 (1987)
ortho-Aminoazotoluene	*8*, 61 (1975) (*corr. 42*, 254); *Suppl. 7*, 56 (1987)
para-Aminobenzoic acid	*16*, 249 (1978); *Suppl. 7*, 56 (1987)
4-Aminobiphenyl	*1*, 74 (1972) (*corr. 42*, 251); *Suppl. 7*, 91 (1987); *99*, 71 (2010)
2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (*see* MeIQ)	
2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (*see* MeIQx)	
3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (*see* Trp-P-1)	
2-Aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole (*see* Glu-P-2)	
1-Amino-2-methylanthraquinone	*27*, 199 (1982); *Suppl. 7*, 57 (1987)
2-Amino-3-methylimidazo[4,5-*f*]quinoline (*see* IQ)	
2-Amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole (*see* Glu-P-1)	
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (*see* PhIP)	
2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (*see* MeA-α-C)	
3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (*see* Trp-P-2)	
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	*7*, 143 (1974); *Suppl. 7*, 57 (1987)
2-Amino-4-nitrophenol	*57*, 167 (1993)
2-Amino-5-nitrophenol	*57*, 177 (1993)
4-Amino-2-nitrophenol	*16*, 43 (1978); *Suppl. 7*, 57 (1987)
2-Amino-5-nitrothiazole	*31*, 71 (1983); *Suppl. 7*, 57 (1987)
2-Amino-9*H*-pyrido[2,3-*b*]indole (see A-α-C)	
11-Aminoundecanoic acid	*39*, 239 (1986); *Suppl. 7*, 57 (1987)
Amitrole	*7*, 31 (1974); *41*, 293 (1986) (*corr. 52*, 513; *Suppl. 7*, 92 (1987); *79*, 381 (2001)
Ammonium potassium selenide (*see* Selenium and selenium compounds)	
Amorphous silica (*see also* Silica)	*42*, 39 (1987); *Suppl. 7*, 341 (1987); *68*, 41 (1997) (*corr. 81*, 383)
Amosite (*see* Asbestos)	
Ampicillin	*50*, 153 (1990)
Amsacrine	*76*, 317 (2000)
Anabolic steroids (*see* Androgenic (anabolic) steroids)	
Anaesthetics, volatile	*11*, 285 (1976); *Suppl. 7*, 93 (1987)
Analgesic mixtures containing phenacetin (*see also* Phenacetin)	*Suppl. 7*, 310 (1987)
Androgenic (anabolic) steroids	*Suppl. 7*, 96 (1987)
Angelicin and some synthetic derivatives (*see also* Angelicins)	*40*, 291 (1986)

CUMULATIVE INDEX   421

422   IARC MONOGRAPHS VOLUME 93

B

Barium chromate (*see* Chromium and chromium compounds)	
Basic chromic sulfate (*see* Chromium and chromium compounds)	
BCNU (*see* Bischloroethyl nitrosourea)	
11*H*-Benz[*bc*]aceanthrylene	*92*, 35 (2010)
Benz[*j*]aceanthrylene	*92*, 35 (2010)
Benz[*l*]aceanthrylene	*92*, 35 (2010)
Benz[*a*]acridine	*32*, 123 (1983); *Suppl. 7*, 58 (1987)
Benz[*c*]acridine	*3*, 241 (1973); *32*, 129 (1983); *Suppl. 7*, 58 (1987)
Benzal chloride (*see also* α-Chlorinated toluenes and benzoyl chloride)	*29*, 65 (1982); *Suppl. 7*, 148 (1987); *71*, 453 (1999)
Benz[*a*]anthracene	*3*, 45 (1973); *32*, 135 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzene	*7*, 203 (1974) (*corr. 42*, 254); *29*, 93, 391 (1982); *Suppl. 7*, 120 (1987)
Benzidine	*1*, 80 (1972); *29*, 149, 391 (1982); *Suppl. 7*, 123 (1987); *99*, 139 (2010)
Benzidine-based dyes	*Suppl. 7*, 125 (1987); *99*, 249 (2010)
Benzo[*b*]chrysene	*92*, 35 (2010)
Benzo[*g*]chrysene	*92*, 35 (2010)
Benzo[*a*]fluoranthene	*92*, 35 (2010)
Benzo[*b*]fluoranthene	*3*, 69 (1973); *32*, 147 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*j*]fluoranthene	*3*, 82 (1973); *32*, 155 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*k*]fluoranthene	*32*, 163 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*ghi*]fluoranthene	*32*, 171 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*a*]fluorene	*32*, 177 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*b*]fluorene	*32*, 183 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*c*]fluorene	*32*, 189 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzofuran	*63*, 431 (1995)
Benzo[*ghi*]perylene	*32*, 195 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*c*]phenanthrene	*32*, 205 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*a*]pyrene	*3*, 91 (1973); *32*, 211 (1983); (*corr. 68*, 477); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
Benzo[*e*]pyrene	*3*, 137 (1973); *32*, 225 (1983); *Suppl. 7*, 58 (1987); *92*, 35 (2010)
1,4-Benzoquinone (*see para*-Quinone)	
1,4-Benzoquinone dioxime	*29*, 185 (1982); *Suppl. 7*, 58 (1987); *71*, 1251 (1999)
Benzotrichloride (*see also* α-Chlorinated toluenes and benzoyl chloride)	*29*, 73 (1982); *Suppl. 7*, 148 (1987); *71*, 453 (1999)
Benzoyl chloride (*see also* α-Chlorinated toluenes and benzoyl chloride)	*29*, 83 (1982) (*corr. 42*, 261); *Suppl. 7*, 126 (1987); *71*, 453 (1999)

CUMULATIVE INDEX   423

CUMULATIVE INDEX   425

CUMULATIVE INDEX   427

428   IARC MONOGRAPHS VOLUME 93

Conjugated equine oestrogens	*72*, 399 (1999)
Conjugated oestrogens (*see also* Steroidal oestrogens)	*21*, 147 (1979); *Suppl. 7*, 283 (1987)
Continuous glass filament (*see* Man-made vitreous fibres)	
Copper 8-hydroxyquinoline	*15*, 103 (1977); *Suppl. 7*, 61 (1987)
Coronene	*32*, 263 (1983); *Suppl. 7*, 61 (1987); *92*, 35 (2010)
Coumarin	*10*, 113 (1976); *Suppl. 7*, 61 (1987); *77*, 193 (2000)
Creosotes (*see also* Coal-tars)	*35*, 83 (1985); *Suppl. 7*, 177 (1987); *92*, 35 (2010)
meta-Cresidine	*27*, 91 (1982); *Suppl. 7*, 61 (1987)
para-Cresidine	*27*, 92 (1982); *Suppl. 7*, 61 (1987)
Cristobalite (*see* Crystalline silica)	
Crocidolite (*see* Asbestos)	
Crotonaldehyde	*63*, 373 (1995) (*corr. 65*, 549)
Crude oil	*45*, 119 (1989)
Crystalline silica (*see also* Silica)	*42*, 39 (1987); *Suppl. 7*, 341 (1987); *68*, 41 (1997) (*corr. 81*, 383)
Cycasin (*see also* Methylazoxymethanol)	*1*, 157 (1972) (*corr. 42*, 251); *10*, 121 (1976); *Suppl. 7*, 61 (1987)
Cyclamates	*22*, 55 (1980); *Suppl. 7*, 178 (1987); *73*, 195 (1999)
Cyclamic acid (*see* Cyclamates)	
Cyclochlorotine	*10*, 139 (1976); *Suppl. 7*, 61 (1987)
Cyclohexanone	*47*, 157 (1989); *71*, 1359 (1999)
Cyclohexylamine (*see* Cyclamates)	
4--Cyclopenta[*def*]chrysene	*92*, 35 (2010)
Cyclopenta[*cd*]pyrene	*32*, 269 (1983); *Suppl. 7*, 61 (1987); *92*, 35 (2010)
5,6-Cyclopenteno-1,2-benzanthracene	*92*, 35 (2010)
Cyclopropane (*see* Anaesthetics, volatile)	
Cyclophosphamide	*9*, 135 (1975); *26*, 165 (1981); *Suppl. 7*, 182 (1987)
Cyclosporine	*50*, 77 (1990)
Cyproterone acetate	*72*, 49 (1999)

D

2,4-D (*see also* Chlorophenoxy herbicides; Chlorophenoxy herbicides, occupational exposures to)	*15*, 111 (1977)
Dacarbazine	*26*, 203 (1981); *Suppl. 7*, 184 (1987)
Dantron	*50*, 265 (1990) (*corr. 59*, 257)
D&C Red No. 9	*8*, 107 (1975); *Suppl. 7*, 61 (1987); *57*, 203 (1993)
Dapsone	*24*, 59 (1980); *Suppl. 7*, 185 (1987)
Daunomycin	*10*, 145 (1976); *Suppl. 7*, 61 (1987)
DDD (*see* DDT)	
DDE (*see* DDT)	
DDT	*5*, 83 (1974) (*corr. 42*, 253); *Suppl. 7*, 186 (1987); *53*, 179 (1991)
Decabromodiphenyl oxide	*48*, 73 (1990); *71*, 1365 (1999)
Deltamethrin	*53*, 251 (1991)

CUMULATIVE INDEX   429

CUMULATIVE INDEX 431

432   IARC MONOGRAPHS VOLUME 93

Direct Brown 95 (*see also* Benzidine-based dyes)   *29*, 321 (1982)
Disperse Blue 1   *48*, 139 (1990)
Disperse Yellow 3   *8*, 97 (1975); *Suppl. 7*, 60 (1987); *48*, 149 (1990)
Disulfiram   *12*, 85 (1976); *Suppl. 7*, 63 (1987)
Dithranol   *13*, 75 (1977); *Suppl. 7*, 63 (1987)
Divinyl ether (*see* Anaesthetics, volatile)
Doxefazepam   *66*, 97 (1996)
Doxylamine succinate   *79*, 145 (2001)
Droloxifene   *66*, 241 (1996)
Dry cleaning   *63*, 33 (1995)
Dulcin   *12*, 97 (1976); *Suppl. 7*, 63 (1987)
Dyes metabolized to benzidine   *99*, 249 (2010)

E

Endrin   *5*, 157 (1974); *Suppl. 7*, 63 (1987)
Enflurane (*see* Anaesthetics, volatile)
Eosin   *15*, 183 (1977); *Suppl. 7*, 63 (1987)
Epichlorohydrin   *11*, 131 (1976) (*corr. 42*, 256); *Suppl. 7*, 202 (1987); *71*, 603 (1999)
1,2-Epoxybutane   *47*, 217 (1989); *71*, 629 (1999)
1-Epoxyethyl-3,4-epoxycyclohexane (*see* 4-Vinylcyclohexene diepoxide)
3,4-Epoxy-6-methylcyclohexylmethyl 3,4-epoxy-6-methyl-   *11*, 147 (1976); *Suppl. 7*, 63 (1987); *71*, cyclohexane carboxylate   1441 (1999)
cis-9,10-Epoxystearic acid   *11*, 153 (1976); *Suppl. 7*, 63 (1987); *71*, 1443 (1999)
Epstein-Barr virus   *70*, 47 (1997)
d-Equilenin   *72*, 399 (1999)
Equilin   *72*, 399 (1999)
Erionite   *42*, 225 (1987); *Suppl. 7*, 203 (1987)
Estazolam   *66*, 105 (1996)
Ethinyloestradiol   *6*, 77 (1974); *21*, 233 (1979); *Suppl. 7*, 286 (1987); *72*, 49 (1999)
Ethionamide   *13*, 83 (1977); *Suppl. 7*, 63 (1987)
Ethyl acrylate   *19*, 57 (1979); *39*, 81 (1986); *Suppl. 7*, 63 (1987); *71*, 1447 (1999)
Ethyl carbamate   *7,* 111 (1974); *Suppl. 7*, 73 (1987); *96* (2010)
Ethylbenzene   *77*, 227 (2000)
Ethylene   *19*, 157 (1979); *Suppl. 7*, 63 (1987); *60*, 45 (1994); *71*, 1447 (1999)
Ethylene dibromide   *15*, 195 (1977); *Suppl. 7*, 204 (1987); *71*, 641 (1999)
Ethylene oxide   *11*, 157 (1976); *36*, 189 (1985) (*corr. 42*, 263); *Suppl. 7*, 205 (1987); *60*, 73 (1994); *97*, 185 (2008)
Ethylene sulfide   *11*, 257 (1976); *Suppl. 7*, 63 (1987)
Ethylenethiourea   *7,* 45 (1974); *Suppl. 7*, 207 (1987); *79*, 659 (2001)
2-Ethylhexyl acrylate   *60*, 475 (1994)
Ethyl methanesulfonate   *7*, 245 (1974); *Suppl. 7*, 63 (1987)

CUMULATIVE INDEX 433

Fusarenone-X (*see* Toxins derived from *Fusarium graminearum*,
   F. culmorum and *F. crookwellense*)
Fusarin C (*see* Toxins derived from *Fusarium moniliforme*)

G

Gallium arsenide	*86*, 163 (2006)
Gamma (γ)-radiation	*75*, 121 (2000)
Gasoline	*45*, 159 (1989) (*corr. 47*, 505)
Gasoline engine exhaust (*see* Diesel and gasoline engine exhausts)	
Gemfibrozil	*66*, 427 (1996)
Glass fibres (*see* Man-made mineral fibres)	
Glass manufacturing industry, occupational exposures in	*58*, 347 (1993)
Glass wool (*see* Man-made vitreous fibres)	
Glass filaments (*see* Man-made mineral fibres)	
Glu-P-1	*40*, 223 (1986); *Suppl. 7*, 64 (1987)
Glu-P-2	*40*, 235 (1986); *Suppl. 7*, 64 (1987)
L-Glutamic acid, 5-[2-(4-hydroxymethyl)phenylhydrazide] (*see* Agaritine)	
Glycidaldehyde	*11*, 175 (1976); *Suppl. 7*, 64 (1987); *71*, 1459 (1999)
Glycidol	*77*, 469 (2000)
Glycidyl ethers	*47*, 237 (1989); *71*, 1285, 1417, 1525, 1539 (1999)
Glycidyl oleate	*11*, 183 (1976); *Suppl. 7*, 64 (1987)
Glycidyl stearate	*11*, 187 (1976); *Suppl. 7*, 64 (1987)
Griseofulvin	*10*, 153 (1976); *Suppl. 7*, 64, 391 (1987); *79*, 289 (2001)
Guinea Green B	*16*, 199 (1978); *Suppl. 7*, 64 (1987)
Gyromitrin	*31*, 163 (1983); *Suppl. 7*, 64, 391 (1987)

H

Haematite	*1*, 29 (1972); *Suppl. 7*, 216 (1987)
Haematite and ferric oxide	*Suppl. 7*, 216 (1987)
Haematite mining, underground, with exposure to radon	*1*, 29 (1972); *Suppl. 7*, 216 (1987)
Hairdressers and barbers (occupational exposure as)	*57*, 43 (1993); *99*, 487 (2010)
Hair dyes, epidemiology of	*16*, 29 (1978); *27*, 307 (1982); *99*, 487 (2010)
Halogenated acetonitriles	*52*, 269 (1991); *71*, 1325, 1369, 1375, 1533 (1999)
Halothane (*see* Anaesthetics, volatile)	
HC Blue No. 1	*57*, 129 (1993)
HC Blue No. 2	*57*, 143 (1993)
α-HCH (*see* Hexachlorocyclohexanes)	
β-HCH (*see* Hexachlorocyclohexanes)	
γ-HCH (*see* Hexachlorocyclohexanes)	
HC Red No. 3	*57*, 153 (1993)
HC Yellow No. 4	*57*, 159 (1993)
Heating oils (*see* Fuel oils)	
Helicobacter pylori (infection with)	*61*, 177 (1994)
Hepatitis B virus	*59*, 45 (1994)

CUMULATIVE INDEX   435

436   IARC MONOGRAPHS VOLUME 93

IQ	*40*, 261 (1986); *Suppl. 7*, 64 (1987); *56*, 165 (1993)
Iron and steel founding	*34*, 133 (1984); *Suppl. 7*, 224 (1987)
Iron-dextran complex	*2*, 161 (1973); *Suppl. 7*, 226 (1987)
Iron-dextrin complex	*2*, 161 (1973) (*corr. 42*, 252); *Suppl. 7*, 64 (1987)
Iron oxide (*see* Ferric oxide)	
Iron oxide, saccharated (*see* Saccharated iron oxide)	
Iron sorbitol-citric acid complex	*2*, 161 (1973); *Suppl. 7*, 64 (1987)
Isatidine	*10*, 269 (1976); *Suppl. 7*, 65 (1987)
Isoflurane (*see* Anaesthetics, volatile)	
Isoniazid (*see* Isonicotinic acid hydrazide)	
Isonicotinic acid hydrazide	*4*, 159 (1974); *Suppl. 7*, 227 (1987)
Isophosphamide	*26*, 237 (1981); *Suppl. 7*, 65 (1987)
Isoprene	*60*, 215 (1994); *71*, 1015 (1999)
Isopropanol	*15*, 223 (1977); *Suppl. 7*, 229 (1987); *71*, 1027 (1999)
Isopropanol manufacture (strong-acid process) (*see also* Isopropanol; Sulfuric acid and other strong inorganic acids, occupational exposures to mists and vapours from)	*Suppl. 7*, 229 (1987)
Isopropyl oils	*15*, 223 (1977); *Suppl. 7*, 229 (1987); *71*, 1483 (1999)
Isosafrole	*1*, 169 (1972); *10*, 232 (1976); *Suppl. 7*, 65 (1987)

J

Jacobine	*10*, 275 (1976); *Suppl. 7*, 65 (1987)
Jet fuel	*45*, 203 (1989)
Joinery (*see* Carpentry and joinery)	

K

Kaempferol	*31*, 171 (1983); *Suppl. 7*, 65 (1987)
Kaposi's sarcoma herpesvirus	*70*, 375 (1997)
Kepone (see Chlordecone)	
Kojic acid	*79*, 605 (2001)

L

Lasiocarpine	*10*, 281 (1976); *Suppl. 7*, 65 (1987)
Lauroyl peroxide	*36*, 315 (1985); *Suppl. 7*, 65 (1987); *71*, 1485 (1999)
Lead acetate (*see* Lead and lead compounds)	
Lead and lead compounds (*see also* Foreign bodies)	*1*, 40 (1972) (*corr. 42*, 251); *2*, 52, 150 (1973); *12*, 131 (1976); *23*, 40, 208, 209, 325 (1980); *Suppl. 7*, 230 (1987); *87* (2006)
Lead arsenate (*see* Arsenic and arsenic compounds)	
Lead carbonate (*see* Lead and lead compounds)	
Lead chloride (*see* Lead and lead compounds)	
Lead chromate (*see* Chromium and chromium compounds)	

CUMULATIVE INDEX 437

438   IARC MONOGRAPHS VOLUME 93

Melamine   *39*, 333 (1986); *Suppl. 7*, 65 (1987); *73*, 329
                                                         (1999)
Melphalan   *9*, 167 (1975); *Suppl. 7*, 239 (1987)
6-Mercaptopurine   *26*, 249 (1981); *Suppl. 7*, 240 (1987)
Mercuric chloride (*see* Mercury and mercury compounds)
Mercury and mercury compounds   *58*, 239 (1993)
Merphalan   *9*, 169 (1975); *Suppl. 7*, 65 (1987)
Mestranol   *6*, 87 (1974); *21*, 257 (1979) (*corr. 42*, 259);
                                                         Suppl. 7, 288 (1987); *72*, 49 (1999)

Metabisulfites (*see* Sulfur dioxide and some sulfites, bisulfites
    and metabisulfites)
Metallic mercury (*see* Mercury and mercury compounds)
Methanearsonic acid, disodium salt (*see* Arsenic and arsenic
    compounds)
Methanearsonic acid, monosodium salt (*see* Arsenic and arsenic
    compounds)
Methimazole   *79*, 53 (2001)
Methotrexate   *26*, 267 (1981); *Suppl. 7*, 241 (1987)
Methoxsalen (*see* 8-Methoxypsoralen)
Methoxychlor   *5*, 193 (1974); *20*, 259 (1979); *Suppl. 7*, 66
                                                         (1987)
Methoxyflurane (*see* Anaesthetics, volatile)
5-Methoxypsoralen   *40*, 327 (1986); *Suppl. 7*, 242 (1987)
8-Methoxypsoralen (*see also* 8-Methoxypsoralen plus ultraviolet   *24*, 101 (1980)
    radiation)
8-Methoxypsoralen plus ultraviolet radiation   *Suppl. 7*, 243 (1987)
Methyl acrylate   *19*, 52 (1979); *39*, 99 (1986); *Suppl. 7*, 66
                                                         (1987); *71*, 1489 (1999)
5-Methylangelicin plus ultraviolet radiation (*see also* Angelicin   *Suppl. 7*, 57 (1987)
    and some synthetic derivatives)
2-Methylaziridine   *9*, 61 (1975); *Suppl. 7*, 66 (1987); *71*, 1497
                                                         (1999)
Methylazoxymethanol acetate (*see also* Cycasin)   *1*, 164 (1972); *10*, 131 (1976); *Suppl. 7*, 66
                                                         (1987)
Methyl bromide   *41*, 187 (1986) (*corr. 45*, 283); *Suppl. 7*, 245
                                                         (1987); *71*, 721 (1999)
Methyl *tert*-butyl ether   *73*, 339 (1999)
Methyl carbamate   *12*, 151 (1976); *Suppl. 7*, 66 (1987)
Methyl-CCNU (*see* 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-
    1-nitrosourea)
Methyl chloride   *41*, 161 (1986); *Suppl. 7*, 246 (1987); *71*, 737
                                                         (1999)
1-, 2-, 3-, 4-, 5- and 6-Methylchrysenes   *32*, 379 (1983); *Suppl. 7*, 66 (1987); *92*, 35
                                                         (2010)
N-Methyl-*N*,4-dinitrosoaniline   *1*, 141 (1972); *Suppl. 7*, 66 (1987)
4,4′-Methylenebis(2-chloroaniline)   *4*, 65 (1974) (*corr. 42*, 252); *Suppl. 7*, 246
                                                         (1987); *57*, 271 (1993); *99*, 313 (2010)
4,4′-Methylenebis(*N*,*N*-dimethyl)benzenamine   *27*, 119 (1982); *Suppl. 7*, 66 (1987)
4,4′-Methylenebis(2-methylaniline)   *4*, 73 (1974); *Suppl. 7*, 248 (1987)
4,4′-Methylenedianiline   *4*, 79 (1974) (*corr. 42*, 252); *39*, 347 (1986);
                                                         Suppl. 7, 66 (1987)
4,4′-Methylenediphenyl diisocyanate   *19*, 314 (1979); *Suppl. 7*, 66 (1987); *71*, 1049
                                                         (1999)

CUMULATIVE INDEX   439

Mordanite (*see* Zeolites)	
Morinda officinalis (*see also* Traditional herbal medicines)	*82*, 129 (2002)
Morpholine	*47*, 199 (1989); *71*, 1511 (1999)
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone	*7*, 161 (1974); *Suppl. 7*, 67 (1987)
Musk ambrette	*65*, 477 (1996)
Musk xylene	*65*, 477 (1996)
Mustard gas	*9,* 181 (1975) (*corr. 42*, 254); *Suppl. 7*, 259 (1987)
Myleran (*see* 1,4-Butanediol dimethanesulfonate)	

N

Nafenopin	*24*, 125 (1980); *Suppl. 7*, 67 (1987)
Naphthalene	*82*, 367 (2002)
1,5-Naphthalenediamine	*27*, 127 (1982); *Suppl. 7*, 67 (1987)
1,5-Naphthalene diisocyanate	*19*, 311 (1979); *Suppl. 7*, 67 (1987); *71*, 1515 (1999)
Naphtho[1,2-*b*]fluoranthene	*92*, 35 (2010)
Naphtho[2,1-*a*]fluoranthene	*92*, 35 (2010)
Naphtho[2,3-*e*]pyrene	*92*, 35 (2010)
1-Naphthylamine	*4*, 87 (1974) (*corr. 42*, 253); *Suppl. 7*, 260 (1987)
2-Naphthylamine	*4*, 97 (1974); *Suppl. 7*, 261 (1987); *99*, 357 (2010)
1-Naphthylthiourea	*30*, 347 (1983); *Suppl. 7*, 263 (1987)
Neutrons	*75*, 361 (2000)
Nickel acetate (*see* Nickel and nickel compounds)	
Nickel ammonium sulfate (*see* Nickel and nickel compounds)	
Nickel and nickel compounds (*see* also Implants, surgical)	*2*, 126 (1973) (*corr. 42*, 252); *11*, 75 (1976); *Suppl. 7*, 264 (1987) (*corr. 45*, 283); *49*, 257 (1990) (*corr. 67*, 395)
Nickel carbonate (*see* Nickel and nickel compounds)	
Nickel carbonyl (*see* Nickel and nickel compounds)	
Nickel chloride (*see* Nickel and nickel compounds)	
Nickel-gallium alloy (*see* Nickel and nickel compounds)	
Nickel hydroxide (*see* Nickel and nickel compounds)	
Nickelocene (*see* Nickel and nickel compounds)	
Nickel oxide (*see* Nickel and nickel compounds)	
Nickel subsulfide (*see* Nickel and nickel compounds)	
Nickel sulfate (*see* Nickel and nickel compounds)	
Niridazole	*13*, 123 (1977); *Suppl. 7*, 67 (1987)
Nithiazide	*31*, 179 (1983); *Suppl. 7*, 67 (1987)
Nitrate or nitrite, ingested, under conditions that result in endogenous nitrosation	*94,* 45 (2010)
Nitrilotriacetic acid and its salts	*48*, 181 (1990); *73*, 385 (1999)
Nitrite (*see* Nitrate or nitrite)	
5-Nitroacenaphthene	*16*, 319 (1978); *Suppl. 7*, 67 (1987)
5-Nitro-*ortho*-anisidine	*27*, 133 (1982); *Suppl. 7,* 67 (1987)
2-Nitroanisole	*65*, 369 (1996)
9-Nitroanthracene	*33*, 179 (1984); *Suppl. 7*, 67 (1987)
7-Nitrobenz[*a*]anthracene	*46*, 247 (1989)
Nitrobenzene	*65*, 381 (1996)

CUMULATIVE INDEX   441

3-(*N*-Nitrosomethylamino)propionaldehyde	*37*, 263 (1985); *Suppl. 7*, 68 (1987); *85*, 281 (2004)
3-(*N*-Nitrosomethylamino)propionitrile	*37*, 263 (1985); *Suppl. 7*, 68 (1987); *85*, 281 (2004)
4-(*N*-Nitrosomethylamino)-4-(3-pyridyl)-1-butanal	*37*, 205 (1985); *Suppl. 7*, 68 (1987)
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	*37*, 209 (1985); *Suppl. 7*, 68 (1987); *89*, 419 (2007)
N-Nitrosomethylethylamine	*17*, 221 (1978); *Suppl. 7*, 68 (1987)
N-Nitroso-*N*-methylurea (*see N*-Methyl-*N*-nitrosourea)	
N-Nitroso-*N*-methylurethane (see *N*-Methyl-*N*-nitrosourethane)	
N-Nitrosomethylvinylamine	*17*, 257 (1978); *Suppl. 7*, 68 (1987)
N-Nitrosomorpholine	*17*, 263 (1978); *Suppl. 7*, 68 (1987)
N′-Nitrosonornicotine (NNN)	*17*, 281 (1978); *37*, 241 (1985); *Suppl. 7*, 68 (1987); *89*, 419 (2007)
N-Nitrosopiperidine	*17*, 287 (1978); *Suppl. 7*, 68 (1987)
N-Nitrosoproline	*17*, 303 (1978); *Suppl. 7*, 68 (1987)
N-Nitrosopyrrolidine	*17*, 313 (1978); *Suppl. 7*, 68 (1987)
N-Nitrososarcosine	*17*, 327 (1978); *Suppl. 7*, 68 (1987)
Nitrosoureas, chloroethyl (*see* Chloroethyl nitrosoureas)	
5-Nitro-*ortho*-toluidine	*48*, 169 (1990)
2-Nitrotoluene	*65*, 409 (1996)
3-Nitrotoluene	*65*, 409 (1996)
4-Nitrotoluene	*65*, 409 (1996)
Nitrous oxide (*see* Anaesthetics, volatile)	
Nitrovin	*31*, 185 (1983); *Suppl. 7*, 68 (1987)
Nivalenol (*see* Toxins derived from *Fusarium graminearum, F. culmorum* and *F. crookwellense*)	
NNK (*see* 4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone)	
NNN (*see N′*-Nitrosonornicotine)	
Nodularins	*94,* 329 (2010)
Nonsteroidal oestrogens	*Suppl. 7*, 273 (1987)
Norethisterone	*6*, 179 (1974); *21*, 461 (1979); *Suppl. 7*, 294 (1987); *72*, 49 (1999)
Norethisterone acetate	*72*, 49 (1999)
Norethynodrel	*6*, 191 (1974); *21*, 461 (1979) (*corr. 42*, 259); *Suppl. 7*, 295 (1987); *72*, 49 (1999)
Norgestrel	*6*, 201 (1974); *21*, 479 (1979); *Suppl. 7*, 295 (1987); *72*, 49 (1999)
Nylon 6	*19*, 120 (1979); *Suppl. 7*, 68 (1987)

O

Ochratoxin A	*10*, 191 (1976); *31*, 191 (1983) (*corr. 42*, 262); *Suppl. 7*, 271 (1987); *56*, 489 (1993)
Oestradiol	*6*, 99 (1974); *21*, 279 (1979); *Suppl. 7*, 284 (1987); *72*, 399 (1999)
Oestradiol-17β (*see* Oestradiol)	
Oestradiol 3-benzoate (*see* Oestradiol)	
Oestradiol dipropionate (*see* Oestradiol)	
Oestradiol mustard	*9*, 217 (1975); *Suppl. 7*, 68 (1987)
Oestradiol valerate (*see* Oestradiol)	
Oestriol	*6*, 117 (1974); *21*, 327 (1979); *Suppl. 7*, 285 (1987); *72*, 399 (1999)

CUMULATIVE INDEX   443

Phenacetin	*13*, 141 (1977); *24*, 135 (1980); *Suppl. 7*, 310 (1987)
Phenanthrene	*32*, 419 (1983); *Suppl. 7*, 69 (1987); *92*, 35 (2010)
Phenazopyridine hydrochloride	*8*, 117 (1975); *24*, 163 (1980) (*corr. 42*, 260); *Suppl. 7*, 312 (1987)
Phenelzine sulfate	*24*, 175 (1980); *Suppl. 7*, 312 (1987)
Phenicarbazide	*12*, 177 (1976); *Suppl. 7*, 70 (1987)
Phenobarbital and its sodium salt	*13*, 157 (1977); *Suppl. 7*, 313 (1987); *79*, 161 (2001)
Phenol	*47*, 263 (1989) (*corr. 50*, 385); *71*, 749 (1999)
Phenolphthalein	*76*, 387 (2000)
Phenoxyacetic acid herbicides (*see* Chlorophenoxy herbicides)	
Phenoxybenzamine hydrochloride	*9*, 223 (1975); *24*, 185 (1980); *Suppl. 7*, 70 (1987)
Phenylbutazone	*13*, 183 (1977); *Suppl. 7*, 316 (1987)
meta-Phenylenediamine	*16*, 111 (1978); *Suppl. 7*, 70 (1987)
para-Phenylenediamine	*16*, 125 (1978); *Suppl. 7*, 70 (1987)
Phenyl glycidyl ether (*see also* Glycidyl ethers)	*71*, 1525 (1999)
N-Phenyl-2-naphthylamine	*16*, 325 (1978) (*corr. 42*, 257); *Suppl. 7*, 318 (1987)
ortho-Phenylphenol	*30*, 329 (1983); *Suppl. 7*, 70 (1987); *73*, 451 (1999)
Phenytoin	*13*, 201 (1977); *Suppl. 7*, 319 (1987); *66*, 175 (1996)
Phillipsite (*see* Zeolites)	
PhIP	*56*, 229 (1993)
Picene	*92*, 35 (2010)
Pickled vegetables	*56*, 83 (1993)
Picloram	*53*, 481 (1991)
Piperazine oestrone sulfate (*see* Conjugated oestrogens)	
Piperonyl butoxide	*30*, 183 (1983); *Suppl. 7*, 70 (1987)
Pitches, coal-tar (*see* Coal-tar pitches)	
Polyacrylic acid	*19*, 62 (1979); *Suppl. 7*, 70 (1987)
Polybrominated biphenyls	*18*, 107 (1978); *41*, 261 (1986); *Suppl. 7*, 321 (1987)
Polychlorinated biphenyls	*7*, 261 (1974); *18*, 43 (1978) (*corr. 42*, 258); *Suppl. 7*, 322 (1987)
Polychlorinated camphenes (*see* Toxaphene)	
Polychlorinated dibenzo-*para*-dioxins (other than 2,3,7,8-tetrachlorodibenzodioxin)	*69*, 33 (1997)
Polychlorinated dibenzofurans	*69*, 345 (1997)
Polychlorophenols and their sodium salts	*71*, 769 (1999)
Polychloroprene	*19*, 141 (1979); *Suppl. 7*, 70 (1987)
Polyethylene (*see also* Implants, surgical)	*19*, 164 (1979); *Suppl. 7*, 70 (1987)
Poly(glycolic acid) (*see* Implants, surgical)	
Polymethylene polyphenyl isocyanate (*see also* 4,4′-Methylenediphenyl diisocyanate)	*19*, 314 (1979); *Suppl. 7*, 70 (1987)
Polymethyl methacrylate (*see also* Implants, surgical)	*19*, 195 (1979); *Suppl. 7*, 70 (1987)
Polyoestradiol phosphate (*see* Oestradiol-17β)	
Polypropylene (*see also* Implants, surgical)	*19*, 218 (1979); *Suppl. 7*, 70 (1987)
Polystyrene (*see also* Implants, surgical)	*19*, 245 (1979); *Suppl. 7*, 70 (1987)
Polytetrafluoroethylene (*see also* Implants, surgical)	*19*, 288 (1979); *Suppl. 7*, 70 (1987)
Polyurethane foams (*see also* Implants, surgical)	*19*, 320 (1979); *Suppl. 7*, 70 (1987)

CUMULATIVE INDEX   445

Q

Quartz (*see* Crystalline silica)
Quercetin (*see also* Bracken fern)   *31*, 213 (1983); *Suppl. 7*, 71 (1987); *73*, 497
                                                    (1999)
para-Quinone   *15*, 255 (1977); *Suppl. 7*, 71 (1987); *71*, 1245
                                                    (1999)
Quintozene   *5*, 211 (1974); *Suppl. 7*, 71 (1987)

R

Radiation (*see* gamma-radiation, neutrons, ultraviolet radiation,
  X-radiation)
Radionuclides, internally deposited   *78* (2001)
Radon   *43*, 173 (1988) (*corr. 45*, 283)
Refractory ceramic fibres (*see* Man-made vitreous fibres)
Reserpine   *10*, 217 (1976); *24*, 211 (1980) (*corr. 42*,
                                                    260); *Suppl. 7*, 330 (1987)
Resorcinol   *15*, 155 (1977); *Suppl. 7*, 71 (1987); *71*, 1119
                                                    (1990)
Retrorsine   *10*, 303 (1976); *Suppl. 7*, 71 (1987)
Rhodamine B   *16*, 221 (1978); *Suppl. 7*, 71 (1987)
Rhodamine 6G   *16*, 233 (1978); *Suppl. 7*, 71 (1987)
Riddelliine   *10*, 313 (1976); *Suppl. 7*, 71 (1987); *82*, 153
                                                    (2002)
Rifampicin   *24*, 243 (1980); *Suppl. 7*, 71 (1987)
Ripazepam   *66*, 157 (1996)
Rock (stone) wool (*see* Man-made vitreous fibres)
Rubber industry   *28* (1982) (*corr. 42*, 261); *Suppl. 7*, 332
                                                    (1987)
Rubia tinctorum (*see also* Madder root, Traditional herbal medicines)   *82*, 129 (2002)
Rugulosin   *40*, 99 (1986); *Suppl. 7*, 71 (1987)

S

Saccharated iron oxide   *2*, 161 (1973); *Suppl. 7*, 71 (1987)
Saccharin and its salts   *22*, 111 (1980) (*corr. 42*, 259); *Suppl. 7*, 334
                                                    (1987); *73*, 517 (1999)
Safrole   *1*, 169 (1972); *10*, 231 (1976); *Suppl. 7*, 71
                                                    (1987)
Salted fish   *56*, 41 (1993)
Sawmill industry (including logging) (*see* Lumber and
  sawmill industry (including logging))
Scarlet Red   *8*, 217 (1975); *Suppl. 7*, 71 (1987)
Schistosoma haematobium (infection with)   *61*, 45 (1994)
Schistosoma japonicum (infection with)   *61*, 45 (1994)
Schistosoma mansoni (infection with)   *61*, 45 (1994)
Selenium and selenium compounds   *9*, 245 (1975) (*corr. 42*, 255); *Suppl. 7*, 71
                                                    (1987)
Selenium dioxide (*see* Selenium and selenium compounds)
Selenium oxide (*see* Selenium and selenium compounds)
Semicarbazide hydrochloride   *12*, 209 (1976) (*corr. 42*, 256); *Suppl. 7*, 71
                                                    (1987)

CUMULATIVE INDEX   447

448   IARC MONOGRAPHS VOLUME 93

Streptozotocin   *4*, 221 (1974); *17*, 337 (1978); *Suppl. 7*, 72
                                                            (1987)
Strobane® (*see* Terpene polychlorinates)
Strong-inorganic-acid mists containing sulfuric acid (*see* Mists and
    vapours from sulfuric acid and other strong inorganic acids)
Strontium chromate (*see* Chromium and chromium compounds)
Styrene   *19*, 231 (1979) (*corr. 42*, 258); *Suppl. 7*, 345
                                                            (1987); *60*, 233 (1994) (*corr. 65*, 549); *82*,
                                                            437 (2002)
Styrene-acrylonitrile copolymers   *19*, 97 (1979); *Suppl. 7*, 72 (1987)
Styrene-butadiene copolymers   *19*, 252 (1979); *Suppl. 7*, 72 (1987)
Styrene-7,8-oxide   *11*, 201 (1976); *19*, 275 (1979); *36*, 245
                                                            (1985); *Suppl. 7*, 72 (1987); *60*, 321 (1994)
Succinic anhydride   *15*, 265 (1977); *Suppl. 7*, 72 (1987)
Sudan I   *8*, 225 (1975); *Suppl. 7*, 72 (1987)
Sudan II   *8*, 233 (1975); *Suppl. 7*, 72 (1987)
Sudan III   *8*, 241 (1975); *Suppl. 7*, 72 (1987)
Sudan Brown RR   *8*, 249 (1975); *Suppl. 7*, 72 (1987)
Sudan Red 7B   *8*, 253 (1975); *Suppl. 7*, 72 (1987)
Sulfadimidine (*see* Sulfamethazine)
Sulfafurazole   *24*, 275 (1980); *Suppl. 7*, 347 (1987)
Sulfallate   *30*, 283 (1983); *Suppl. 7*, 72 (1987)
Sulfamethazine and its sodium salt   *79*, 341 (2001)
Sulfamethoxazole   *24*, 285 (1980); *Suppl. 7*, 348 (1987); *79*, 361
                                                            (2001)
Sulfites (*see* Sulfur dioxide and some sulfites, bisulfites and
metabisulfites)
Sulfur dioxide and some sulfites, bisulfites and metabisulfites   *54*, 131 (1992)
Sulfur mustard (*see* Mustard gas)
Sulfuric acid and other strong inorganic acids, occupational   *54*, 41 (1992)
    exposures to mists and vapours from
Sulfur trioxide   *54*, 121 (1992)
Sulphisoxazole (*see* Sulfafurazole)
Sunset Yellow FCF   *8*, 257 (1975); *Suppl. 7*, 72 (1987)
Symphytine   *31*, 239 (1983); *Suppl. 7*, 72 (1987)

T

2,4,5-T (*see also* Chlorophenoxy herbicides; Chlorophenoxy   *15*, 273 (1977)
    herbicides, occupational exposures to)
Talc   *42*, 185 (1987); *Suppl. 7*, 349 (1987); *93*, 277
                                                            (2010)
Talc, inhaled, not containing asbestos or asbestiform fibres   *93*, 277 (2010)
Talc-based body powder, perineal use of   *93*, 277 (2010)
Tamoxifen   *66*, 253 (1996)
Tannic acid   *10*, 253 (1976) (*corr. 42*, 255); *Suppl. 7*, 72
                                                            (1987)
Tannins (*see also* Tannic acid)   *10*, 254 (1976); *Suppl. 7*, 72 (1987)
TCDD (*see* 2,3,7,8-Tetrachlorodibenzo-para-dioxin)
TDE (*see* DDT)
Tea   *51*, 207 (1991)
Temazepam   *66*, 161 (1996)
Teniposide   *76*, 259 (2000)

CUMULATIVE INDEX 449

ortho-Toluidine	*16*, 349 (1978); *27*, 155 (1982) (*corr. 68*, 477); *Suppl. 7*, 362 (1987); *77*, 267 (2000); *99*, 395 (2010)
Toremifene	*66*, 367 (1996)
Toxaphene	*20*, 327 (1979); *Suppl. 7*, 72 (1987); *79*, 569 (2001)
T-2 Toxin (*see* Toxins derived from *Fusarium sporotrichioides*)	
Toxins derived from *Fusarium graminearum*, *F. culmorum* and *F. crookwellense*	*11*, 169 (1976); *31*, 153, 279 (1983); *Suppl. 7*, 64, 74 (1987); *56*, 397 (1993)
Toxins derived from *Fusarium moniliforme*	*56*, 445 (1993)
Toxins derived from *Fusarium sporotrichioides*	*31*, 265 (1983); *Suppl. 7*, 73 (1987); *56*, 467 (1993)
Traditional herbal medicines	*82*, 41 (2002)
Tremolite (*see* Asbestos)	
Treosulfan	*26*, 341 (1981); *Suppl. 7*, 363 (1987)
Triaziquone (*see* Tris(aziridinyl)-*para*-benzoquinone)	
Trichlorfon	*30*, 207 (1983); *Suppl. 7*, 73 (1987)
Trichlormethine	*9*, 229 (1975); *Suppl. 7*, 73 (1987); *50*, 143 (1990)
Trichloroacetic acid	*63*, 291 (1995) (*corr. 65*, 549); *84* (2004)
Trichloroacetonitrile (*see also* Halogenated acetonitriles)	*71*, 1533 (1999)
1,1,1-Trichloroethane	*20*, 515 (1979); *Suppl. 7*, 73 (1987); *71*, 881 (1999)
1,1,2-Trichloroethane	*20*, 533 (1979); *Suppl. 7*, 73 (1987); *52*, 337 (1991); *71*, 1153 (1999)
Trichloroethylene	*11*, 263 (1976); *20*, 545 (1979); *Suppl. 7*, 364 (1987); *63*, 75 (1995) (*corr. 65*, 549)
2,4,5-Trichlorophenol (*see also* Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	*20*, 349 (1979)
2,4,6-Trichlorophenol (*see also* Chlorophenols; Chlorophenols, occupational exposures to; Polychlorophenols and their sodium salts)	*20*, 349 (1979)
(2,4,5-Trichlorophenoxy)acetic acid (*see* 2,4,5-T)	
1,2,3-Trichloropropane	*63*, 223 (1995)
Trichlorotriethylamine-hydrochloride (*see* Trichlormethine)	
T2-Trichothecene (*see* Toxins derived from *Fusarium sporotrichioides*)	
Tridymite (*see* Crystalline silica)	
Triethanolamine	*77*, 381 (2000)
Triethylene glycol diglycidyl ether	*11*, 209 (1976); *Suppl. 7*, 73 (1987); *71*, 1539 (1999)
Trifluralin	*53*, 515 (1991)
4,4′,6-Trimethylangelicin plus ultraviolet radiation (*see also* Angelicin and some synthetic derivatives)	*Suppl. 7*, 57 (1987)
2,4,5-Trimethylaniline	*27*, 177 (1982); *Suppl. 7*, 73 (1987)
2,4,6-Trimethylaniline	*27*, 178 (1982); *Suppl. 7*, 73 (1987)
4,5′,8-Trimethylpsoralen	*40*, 357 (1986); *Suppl. 7*, 366 (1987)
Trimustine hydrochloride (*see* Trichlormethine)	
2,4,6-Trinitrotoluene	*65*, 449 (1996)
Triphenylene	*32*, 447 (1983); *Suppl. 7*, 73 (1987); *92*, 35 (2010)
Tris(aziridinyl)-*para*-benzoquinone	*9*, 67 (1975); *Suppl. 7*, 367 (1987)
Tris(1-aziridinyl)phosphine-oxide	*9*, 75 (1975); *Suppl. 7*, 73 (1987)

CUMULATIVE INDEX   451

W

Welding	*49*, 447 (1990) (*corr. 52*, 513)
Wollastonite	*42*, 145 (1987); *Suppl. 7*, 377 (1987); *68*, 283 (1997)
Wood dust	*62*, 35 (1995)
Wood industries	*25* (1981); *Suppl. 7*, 378 (1987)

X

X-radiation	*75*, 121 (2000)
Xylenes	*47*, 125 (1989); *71*, 1189 (1999)
2,4-Xylidine	*16*, 367 (1978); *Suppl. 7*, 74 (1987)
2,5-Xylidine	*16*, 377 (1978); *Suppl. 7*, 74 (1987)
2,6-Xylidine (*see* 2,6-Dimethylaniline)	

Y

Yellow AB	*8*, 279 (1975); *Suppl. 7*, 74 (1987)
Yellow OB	*8*, 287 (1975); *Suppl. 7*, 74 (1987)

Z

Zalcitabine	*76*, 129 (2000)
Zearalenone (*see* Toxins derived from *Fusarium graminearum*, *F. culmorum* and *F. crookwellense*)	
Zectran	*12*, 237 (1976); *Suppl. 7*, 74 (1987)
Zeolites other than erionite	*68*, 307 (1997)
Zidovudine	*76*, 73 (2000)
Zinc beryllium silicate (*see* Beryllium and beryllium compounds)	
Zinc chromate (*see* Chromium and chromium compounds)	
Zinc chromate hydroxide (*see* Chromium and chromium compounds)	
Zinc potassium chromate (*see* Chromium and chromium compounds)	
Zinc yellow (*see* Chromium and chromium compounds)	
Zineb	*12*, 245 (1976); *Suppl. 7*, 74 (1987)
Ziram	*12*, 259 (1976); *Suppl. 7*, 74 (1987); *53*, 423 (1991)

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1990; 346 pages (out-of-print)

Exhibit 29

Evolution of the Ultramafic Complexes of Northwestern New England*

ALFRED H. CHIDESTER

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INTRODUCTION

THIS PAPER IS BASED on detailed studies of parts of the belt of ultramafic rocks in Vermont and northwestern Massachusetts (see Fig. 26–1) carried out by the U.S. Geological Survey. In their geotectonic setting, stratigraphic and structural relations, range of variation, and metamorphic features, the ultramafic rock complexes are representative of most of the ultramafic rocks of New England and of many in southeastern Quebec. The aim of the paper is to relate the varied petrologic and structural features of the ultramafic complexes to the tectonic setting, sedimentary environment, and structural and metamorphic history of the belt; and on the basis of these relations to present an interpretation of the evolutionary history of the complexes that accounts for their striking variations and that is generally valid for the ultramafic complexes of New England and southeastern Quebec.

It is gratifying to express here my indebtedness to Professor Marland Billings, who directed and carried out the early part of the U.S. Geological Survey's program of talc investigations in Vermont, in 1944–1945, and who has subsequently maintained a lively interest in these studies that has been very stimulating and helpful. I take pleasure, also, in acknowledging the considerable contributions to this paper of my colleagues in the Vermont studies, Dr. Wallace M. Cady and Prof. Arden L. Albee.

REGIONAL GEOLOGY

The country rocks of the belt of ultramafics are stratigraphically entirely below the unconformity at the base of the Silurian section (see Cady, in press). They comprise phyllite and schist, both of which are locally graphitic and albitic, greenstone or amphibolite, and minor quartzite and impure marble. The lithologic units commonly intergrade rather abruptly by small-scale intertonguing and by change in mineral composition, both parallel and normal to the trends of the units. They represent metamorphosed sedimentary and volcanic rocks that range in probable age from earliest Cambrian to Ordovician. The protoliths of the predominant metamorphosed sedimentary rocks are graywacke and shale. The thickness of the restored section of rocks above the older Precambrian and below the Silurian ranges from 50,000 to 60,000 feet (15,000 to 18,000 m) in central Vermont to less than 35,000 feet (10,000 m) in northern and southern Vermont (see Cady, in press). These features are characteristic of a deeply subsided trough that was rapidly filled with clastic and volcanic rocks —the eugeosynclinal zone of the early to middle Paleozoic orthogeosyncline of the northern Appalachians (see Cady, 1967).

The country rocks of the belt range in metamorphic grade from the greenschist facies to the epidote-amphibolite facies. The rocks are characterized by chlorite, biotite, almandine garnet, epidote, actinolitic hornblende, hornblende, and kyanite, in various combinations appropriate to the metamorphic grade and rock composition.

343

344   CHAPTER 26

The metamorphic grade of these rocks is generally related to the depth of erosion: areas of higher grade are associated with structural highs; of lower grade, with structural lows.

The dominant structural feature of the belt of ultramafic rocks is the Green Mountain anticlinorium (see regional geologic map, this volume; see also Doll et al., 1961). Most of the belt is east of the anticlinorial axis, where the rocks dip chiefly eastward in a steep homoclinal succession, interrupted near the eastern side of the belt by the Worcester and Northfield Mountain
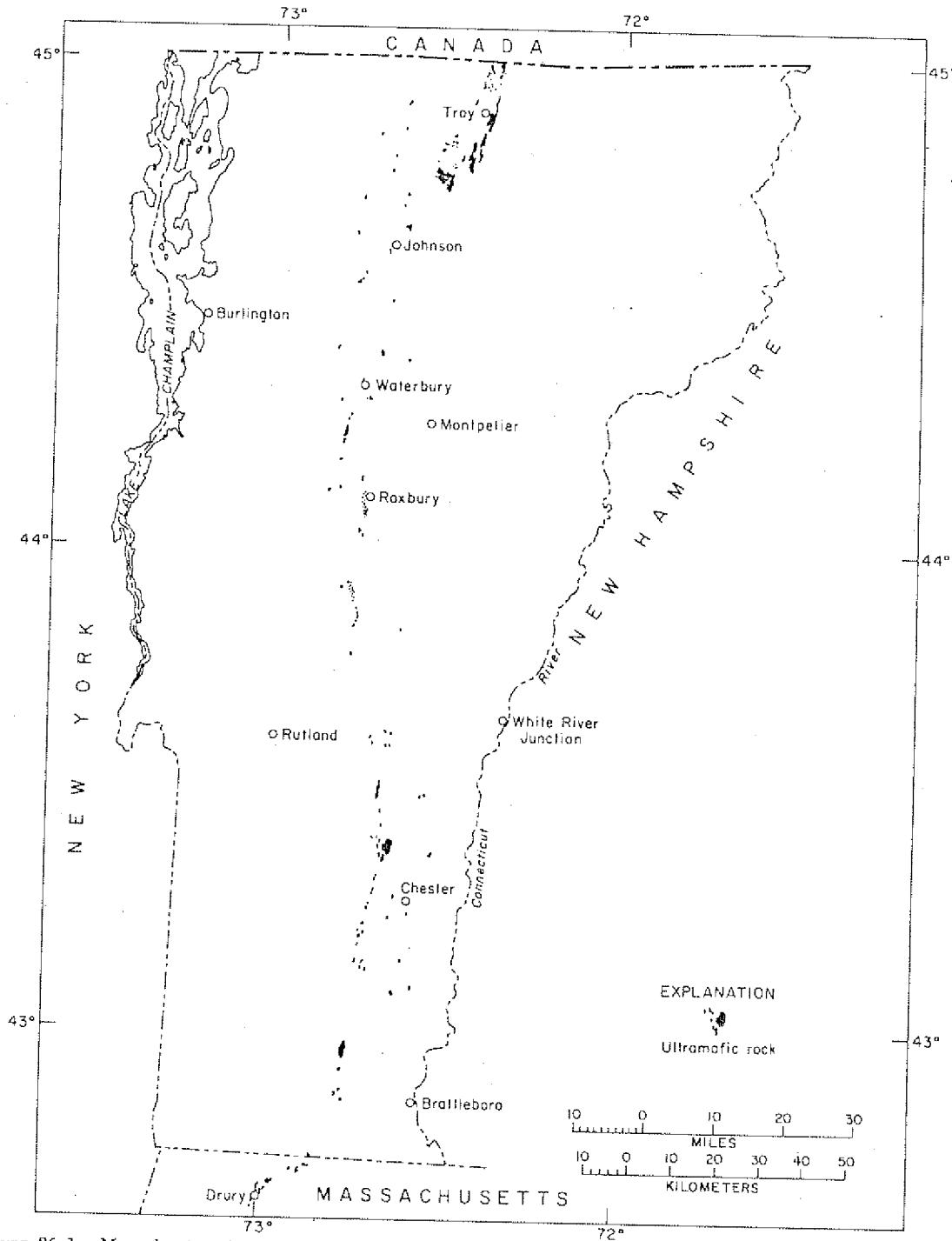
FIGURE 26-1.   Map showing the distribution of ultramafic rocks in Vermont and northwestern Massachusetts.

anticlines in northern and central Vermont, and by several domes in southern Vermont and northwestern Massachusetts. Where the western edge of the belt crosses the anticlinorial axis in northern Vermont, the rocks range through gentle dips to steep westward dips in the west limb.

Two styles of folds, which correspond to two age groups distinguished on the basis of intersecting relations, occur in the belt. The older folds are isoclinal and plastic; their form surfaces are bedding planes. The younger folds are open and nearly parallel (concentric); their form surfaces are schistosity that in most places virtually parallels bedding, but locally transects it markedly. In places, the older (plastic, isoclinal) folds are deformed by the younger (open, parallel) folds, and the axial planes and axial plane schistosity of the older folds are the form surfaces of the younger folds. Slip cleavage parallel to the axial planes of the younger folds transects both bedding schistosity and the "transecting schistosity" that is parallel to the axial planes of the older folds.

Throughout most of the belt, the older folds are only a few inches or a few feet in amplitude and are greatly subordinate to the younger folds. In parts of the belt, however, particularly in northern Vermont, older folds attain amplitudes of tens or hundreds of feet, and locally they have a marked effect on the map pattern. The younger folds are ubiquitous and are related in distribution, pattern, style, and age to the Green Mountain anticlinorium and the Worcester and Northfield Mountain anticlines, whose main stages of development (in Devonian time) essentially coincided with the formation of the domes in southern Vermont and northwestern Massachusetts (see Rosenfeld, this volume).

Faults are generally small and subordinate features of the belt. Most are exposed by mining operations in the immediate vicinity of ultramafic rock complexes, and have only a few feet to a few tens of feet of displacement. Most have a strong strike-slip component, but a few are thrust faults. It is possible that better exposures elsewhere would reveal that such minor faults are common throughout the belt.

GENERAL GEOLOGY OF THE COMPLEXES

The distribution of known ultramafic rocks in Vermont and northwestern Massachusetts is somewhat spotty, but the overall distribution from north to south in the belt is about uniform. The association of greenstone and amphibolite with the belt of ultramafic rocks is striking, but the ultramafics occur in all rock types in the belt. Many occur within greenstone and amphibolite, others are at the upper or lower contact, many others are in schist and phyllite, and some of the larger ultramafic complexes crosscut several rock types.

Other intrusive igneous rocks are rarely associated with the ultramafic complexes. In a few places, thin dikes of camptonite or spessartite (Chidester, 1962, p. 84), and less commonly granite, cut the ultramafic rocks.

The ultramafic complexes are typically podlike or lenticular in form. Their principal planes parallel the regionally dominant transecting schistosity. The bodies range in length from as little as 30 feet (10 m) to as much as 6 miles (10 km), and in thickness from a few tens of feet to as much as 5000 feet (1600 m). Their vertical or down-dip dimension is generally not determined, but in a few, that dimension is known to approach or exceed the strike length exposed at the surface.

The majority of ultramafic complexes are of intermediate size—a few hundred to a thousand feet long and a few tens to a few hundreds of feet thick. They consist typically of a central core of serpentinite, massive at the center and schistose at the margins, surrounded successively outward by a shell of talc-magnesite rock a few inches to as much as 80 feet (25 m) thick and a shell of steatite (talc rock) somewhat variable but generally about 3 feet in thickness. The steatite is adjoined by a "blackwall" alteration zone, consisting in most places of chlorite or successive zones of chlorite and biotite. The smaller ultramafic bodies contain only a small core of schistose serpentinite or consist entirely of talc-magnesite rock and steatite. The very large ultramafic complexes contain, within the serpentinite core, masses of only slightly to moderately serpentinized dunite and minor peridotite, and locally contain appreciable slip- and cross-fiber chrysotile asbestos, in a few places in economic quantities (Cady et al., 1963). Such large complexes locally contain talc-magnesite rock and steatite at the margins and are bordered by blackwall; but in many places such talcose rocks are absent and serpentinite is adjoined by serpentine-chlorite rock and rodingite (calc-silicate rock) rather than blackwall. The two kinds of contact relations are illustrated in Figure 26-2. In addition to the peripheral zones of talcose rocks, many bodies in the intermediate and large size ranges contain tabular masses, as much as 30 feet (10 m) thick, of talc-magnesite rock which locally grades into magnesite rock.

The very large ultramafic complexes in which appreciable dunite and peridotite occur are confined to northern and southern Vermont, where both the accumulation of pre-Silurian eugeosynclinal sediments was thinner than in other parts of the belt and erosion has exposed deeper parts of the section. Smaller, completely serpentinized and extensively steatitized complexes also occur in these parts of the belt. On the other hand, in central Vermont where the sedimentary section is thicker and erosion has not reached so far toward the eugeosynclinal axis, all the complexes are of small to intermediate size and contain no dunite or peridotite.

PETROGRAPHY OF THE COMPLEXES

The minerals and textural features of most of the complexes are predominantly metamorphic in origin, but relict primary textures and minerals are preserved in varying degree. Relict igneous features characterize the serpentinite, talc-magnesite rock, and most of the steatite; poly-metamorphic and relict sedimentary features characterize the contact alteration zones and the outer
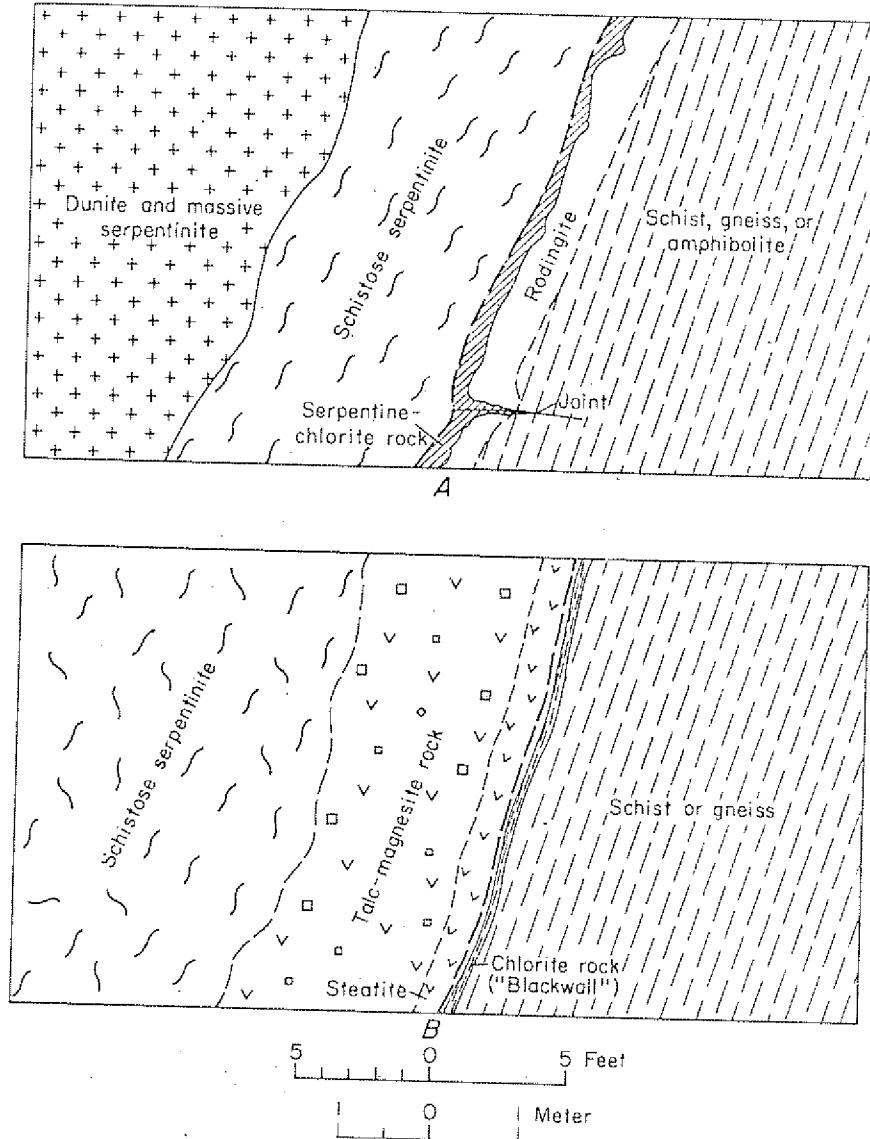
FIGURE 26-2. Diagrammatic sketch maps illustrating the two principal types of zonal relations at the contacts of ultramafic complexes. A, zonation of rodingite (calc-silicate rock) and serpentine-chlorite rock; B, zonation of chlorite rock ("blackwall") and steatite. Heavy broken line marks inferred position of original contact of the intrusive rock.

part of the steatite. The more significant petrographic features are summarized below.

Ultramafic Rocks

Olivine is the principal mineral of the dunite and peridotite, pyroxene is sparse in dunite and minimal in peridotite, and chromite is rare in both. Both dunite and peridotite display layering, marked by differences in mineralogy, color, and texture, from an inch to as much as 3 feet (1 m) thick. The transition from dunite to peridotite is abrupt, but in places is gradational over a few inches. The olivine in both the dunite and peridotite has a sugary granular texture; the pyroxene occurs as small subhedral to anhedral grains. In a few places crystals of olivine as much as 2 inches (5 cm) long display an incipient mosaic pattern like the predominant sugary granular texture, indicating that the sugary granular texture is largely cataclastic in origin. Chromitite occurs sparsely in sharply bounded layers rarely as much as a foot (30 cm) thick.

Massive serpentinite is chiefly antigorite but contains appreciable wispy shreds of chrysotile; schistose serpentinite is almost entirely antigorite. Massive serpentinite displays relict layering and relict textures of the parent igneous rock; schistose serpentinite consists of microscopic to macroscopic chips of randomly oriented platy serpentine (antigorite) separated by thin schistose zones in which the serpentine particles are aligned. The serpentinite displays no discernible evidence of volume change, even where serpentine invades dunite and peridotite in an intricate pattern.

Serpentine veins are of two kinds—asbestiform (chrysotile) and massive or columnar (picrolite); in places the two are intergrown. Each kind occurs both as cross-fiber (or cross-column) and slip-fiber (or slip-column) veins. Veins of cross-fiber habit are virtually confined to dunite, peridotite, and massive serpentinite; of slip-fiber habit, to schistose serpentinite and shear zones. Cross-fiber veins are tabular, wedgelike, or lenticular. They generally have matching walls, and matching irregularities are at opposite ends of individual fibers or columns. Seams of magnetite are common at the vein walls or along partings in the vein. Marginal zones of alteration, composed of chrysotile, antigorite, brucite, and magnetite, are distinctive of cross-fiber veins and are particularly conspicuous in dunite. Slip-fiber veins are small and are distributed along innumerable tiny shear surfaces in schistose serpen-

tinite, except for occasional conspicuous veins in shear zones.

Talc-magnesite displays chiefly metamorphic textures but contains ubiquitous though rare relict chromite. Vestiges of schistosity in the parent serpentinite are common, and in a few places relict layering from parent dunite and massive serpentinite is preserved. Magnesite-quartz rock, which is transitional with talc-magnesite rock, displays much the same textural relations and relict features. Steatite is generally schistose but locally massive. In most steatite, the only relict features are sparse grains of chromite; but adjacent to the blackwall zone, relict textures and minerals of the country rock are common in the steatite.

Rocks of the Contact Alteration Zones

The two types of contact alteration zones that are characteristic of the ultramafic complexes display distinctive associations that appear to be mutually exclusive: the blackwall zone is invariably associated with steatite, and the serpentine-chlorite rock and rodingite zone appears always to adjoin serpentinite without an intervening zone of steatite. These relations hold for contacts of septa and inclusions within the ultramafic bodies as well as for the main contacts of the bodies. In all the contact rocks, where the contact alteration zones cut across layering in the country rock, the undistorted pattern of relict layering in the zones indicates no discernible change in volume.

Rocks of the *blackwall and steatite* association manifest several zonal patterns that primarily reflect grade of metamorphism and composition of the country rock. In the lower greenschist facies, the blackwall in siliceous schist consists essentially of chlorite—highly magnesian next to the steatite, more ferriferous next to the schist; where the schist is albitic, a narrow zone at the outer margin of the blackwall is enriched in albite porphyroblasts, and pseudomorphs after albite are discernible in the pattern of chlorite in the blackwall. Adjacent to greenstone, amphibolite, and impure marble, the blackwall is thin, irregular, and consists of chlorite and tremolite or actinolite; sprays of tremolite also occur in the outer part of the steatite.

With increasing grade of metamorphism, biotite becomes increasingly abundant at the outer margin of the blackwall zone adjacent to siliceous schist, and tremolite increases in the outer part of the steatite zone adjacent to amphibolite. In the upper greenschist facies and the albite-epidote-amphibolite facies, the blackwall in sili-

ceous schist consists of a chlorite zone next to the steatite and a biotite zone next to the schist, each as much as 3–4 inches (10 cm) thick. Next to amphibolite, tremolite is strikingly developed in the outer part of the steatite zone to thicknesses of as much as a foot (25 cm).

Serpentine-chlorite rock and *rodingite* (calc-silicate rock) have a sequential concentric relation to the ultramafic body; locally, however, narrow fingers of serpentine-chlorite rock project beyond the rodingite zone along joints. The serpentine-chlorite rock zone is rather uniformly 1–3 in. (3–8 cm) thick. The thickness of the rodingite zone varies with the composition of the country rock and with structural relations: next to siliceous schist, the rodingite is about 3 feet (1 m) thick; next to amphibolite, 2–12 inches (5–30 cm); at strongly crosscutting contacts where the country rock is sheared and faulted, as much as 10 feet (3 m).

Serpentine-chlorite is uniformly fine-grained and massive. Serpentine predominates over chlorite at the inner margin of the zone, next to serpentinite, and chlorite predominates in the outer part, next to rodingite. In the outer part, also, relict minerals and textures of the rodingite increase toward the rodingite in a transition zone a few millimeters thick. Rodingite varies widely in grain size (from fine to coarse) and in mineralogy. Two to five of the following minerals constitute distinctive assemblages: diopside, clinozoisite, zoisite, grossularite, vesuvianite, prehnite, chlorite, calcite, and magnetite. Diopside and clinozoisite predominate at the inner margin of the rodingite, chlorite and clinozoisite at the outer margin; garnet and vesuvianite are most abundant at the inner margin. Other variations reflect chiefly original differences in composition of relict beds.

STRUCTURAL FEATURES OF THE COMPLEXES

Structural elements of the ultramafic complexes include primary igneous features, features inferred to be related to emplacement, and features related to the post-emplacement history of the complexes. The relations between these features, and between them and the regional structural features, are critical to interpreting the history of the complexes.

The contacts of the ultramafic complexes are chiefly concordant with the regionally dominant transecting schistosity, which bears an axial-plane relation to the older folds. In most places the contacts are also virtually parallel to bedding schistosity; but locally, near older folds, they diverge markedly from bedding, as does the transecting schistosity. The contacts crosscut the transecting schistosity in a step-wise manner, to result in cumulative discordancies up to several tens of feet. At many places, such crosscutting starts at small older folds, where bedding and transecting schistosity diverge. In a few localities where older folds as much as a few hundred feet in amplitude are conspicuous, the contacts of the complexes conform to the gross pattern of the folds but crosscut the bedding schistosity in detail.

Tabular septa and irregular inclusions of country rock in the ultramafic rocks are minor but locally conspicuous features of the complexes. All the septa have the same kind of schistosity as the country rock, and most are tabular parallel to the transecting schistosity. Many of the septa are either attached at one end to the wallrock, or their place of detachment can be inferred with fair confidence. However, many of the xenoliths, particularly the smaller ones, cannot be matched with the nearby wallrock.

Layering in dunite, peridotite, and massive serpentinite is generally subparallel to nearby contacts of the ultramafic complexes or to the inferred attitude of hanging walls that have been eroded away. Marked departures from this relation are associated with zones of pronounced shearing and faulting.

Schistose serpentinite, which occurs at the margins of a central core of massive serpentinite, or which in the smaller bodies constitutes the entire serpentinite mass, contains distinctive features that have been termed shear polyhedra (see Chidester and others, 1951, p. 7; Chidester, 1962, p. 24, 71). These consist of irregular, close-packed polyhedral units of massive serpentinite surrounded by thin, irregular shells of schistose serpentinite. The size of the polyhedra is irregular, but tends to decrease toward the outer part of the serpentinite mass. In the outermost parts, the massive units are commonly reduced to small chips in a schistose matrix, and the serpentinite has a pervading irregular schistosity generally parallel to the walls of the complex.

In contrast to the concentric zones of schistose serpentinite, the tabular zones of sheared serpentinite commonly transect boundaries between dunite, massive serpentinite, and sheared serpentinite. The serpentinite in the shear zones generally has a crude and irregular schistosity approximately parallel to the trend of the shear zones. In a few well-defined and regular shear zones, two dominant conjugate shear surfaces intersect in a rhombic pattern whose long axis is

about parallel to the trend of the shear zone. The tabular zones of sheared serpentinite transect the schistosity of the marginally distributed sheared serpentinite.

The contacts of most ultramafic complexes are not noticeably affected by open folds of the younger set, because throughout most of the belt younger folds of more than a few inches amplitude are sparse. However, in favorable structural situations, such as near the crest of the Green Mountain anticlinorium and in the vicinity of subsidiary anticlines and synclines, contacts of the complexes are strongly folded in conformity with the younger folds in the country rock. In a few strongly folded bodies that have been almost completely altered to talc-carbonate rock and steatite, folds in the hanging wall (the footwall is commonly not well exposed by mining operations) display a characteristic peculiar form: The anticlinal crests are sharp, almost knife-edge, whereas the synclinal troughs are broadly rounded; the resultant profile is like that of oscillation ripple marks. Not uncommonly, steatite is injected a few inches into the country rock along the sharply angled anticlinal crest.

Where the contacts of ultramafic complexes are affected by the younger folds, the layering in dunite, peridotite, and massive serpentinite, and the schistosity in sheared serpentinite, are also folded. Though similar in pattern to the folds in the country rock, these folds in the ultramafic rocks are more diversely oriented.

Schistosity and cleavage related to the younger folds are rare and poorly developed in the ultramafic rocks. In a few places, the schistose serpentinite adjacent to highly folded wallrock displays a pronounced, though widely spaced, slip cleavage parallel to the axial planes of the folds. Steatite has a very pronounced schistosity parallel to the prevailing transecting schistosity in the adjacent wallrock, but only rarely displays a cleavage parallel to the axial planes of the younger folds. Where such cleavage is present it is a crude, widely spaced fracture cleavage that fans 10° or more from parallelism with the axial planes.

Faults in the ultramafic complexes are confined mainly to the vicinity of the contacts (see above, under "Regional Geology"), and generally die out into shear zones. In a few places, sharply bounded faults offset contacts of the complexes by several tens to a few hundreds of feet.

Joints are generally inconspicuous features of the ultramafic rocks. Sets of conjugate joints locally control the distribution of some cross-fiber asbestos veins, but they show no systematic relation to regional structures. The rare but striking talc-carbonate veins are controlled by sets of nearly horizontal and nearly vertical joints.

ORIGIN OF THE ULTRAMAFIC IGNEOUS ROCKS

Although most of the ultramafic complexes contain little or no unmetamorphosed igneous rock, large masses of relatively fresh igneous rock are present in some of the complexes. This fact, together with the distribution of relict igneous minerals in the serpentinite and talcose rocks, indicates an igneous parentage for most of the ultramafic rocks; relict textures and minerals indicate that only small amounts of the rocks in the complexes are derived from the metamorphic country rocks. Consequently, an account of the evolution of the ultramafic complexes depends on the mode of origin postulated for the igneous rocks, which remains highly speculative.

The intergradational layered relations of the dunite, peridotite, and chromitite suggest that they were formed by gravity accumulation during rhythmically varied crystallization of a somewhat more complex magma. Some of the thinner, discontinuous, compositionally different layers may have formed by shearing of the solidified mass during transport under orogenic stress. Similar relict layering in the massive serpentinite, in many of the larger shear polyhedra, and in some of the talc-carbonate rock, suggests that the protolith of all the derivative ultramafic rocks was similarly formed.

The near coincidence of the belt of ultramafic rocks with that of abundant metamorphosed mafic volcanic rocks and its location in the eugeosynclinal zone of the early Paleozoic orthogeosyncline suggests a genetic relation between the ultramafic plutonic rocks and the mafic volcanic rocks. Two kinds of genetic association appear to be almost equally plausible. One model postulates that the ultramafic igneous rocks were formed by accumulation from a complex basaltic magma of unspecified origin, that the liquid fraction was extruded as volcanic materials and intercalated with sediments in the geosynclinal section, and that the ultramafic cumulates were emplaced tectonically during subsequent orogeny. The other model postulates that the mafic volcanic rocks were formed during early stages of partial fusion of the upper mantle during downbuckling of the early Paleozoic geosyncline, and that the ultramafic rocks were formed during the later stages of fusion.

Each model allows for many variations on the central theme, but all versions are similar when modified to take into account the geologic rela-

tious of the complexes and the tectonic history of the belt. Both basic models must account for the rhythmically varied layering of the dunite, peridotite, and chromitite, and both must be compatible with the active orogenic setting. The two models differ chiefly in the postulated composition of the magma from which the ultramafic rocks were immediately derived. The postulated composition depends on the role assigned to partial fusion of the deep crustal or upper mantle rocks.

EMPLACEMENT AND STRUCTURAL HISTORY OF THE ULTRAMAFIC ROCKS

The locally cross-cutting relations of the contacts of the ultramafic complexes and the prevalence of septa and inclusions of country rock in the complexes indicate that the ultramafic rocks were emplaced by forceful intrusion. The general concordance of the contacts with the dominant transecting schistosity that is parallel to the axial planes of the early folds, the cross-cutting of early folds by the contacts, and the control exercised by transecting schistosity on the shape of septa and inclusions of country rock, all demonstrate that the ultramafic rocks were emplaced after the early stage of folding. The general absence of high-temperature contact-metamorphic zones at the margins of the bodies, the peripheral distribution of sheared serpentinite, the shear polyhedra in the schistose serpentinite, and the cataclastic texture of the dunite, further indicate that the ultramafic rocks were emplaced in the solid state at temperatures not much different from those of the enclosing wallrocks; however, variations in contact relations suggest small but significant differences in the temperature of different ultramafic rock bodies at the time of emplacement. Layering in dunite and peridotite suggests that such layered units were carried along essentially intact in the central parts of the larger masses of cumulates, mechanically buffered by yielding in the marginal zones.

The mechanism by which the ultramafic rocks were emplaced in the solid state at their present sites is believed to be intimately related to the process of serpentinization, and is discussed below in more detail under "Origin of the Metamorphic Rocks and Veins."

The conformity of the contacts of the complexes with the pattern of younger folds, and the presence in schistose serpentinite of slip cleavage parallel to the axial planes of these folds, demonstrate that the more recent period of folding was later than the emplacement of the ultramafic

rocks. The local presence in the steatite of a weak fracture cleavage parallel to the axial planes of younger folds suggests that the last stages of the later folding may have extended into the period of steatitization of the complexes. Minor faulting, shearing, and jointing took place chiefly during the late stages of the later period of folding, but locally occurred after folding had virtually ceased. During this stage, joints and fractures were formed extensively in dunite and massive serpentinite, and transecting shear zones were formed in the ultramafic complexes.

ORIGIN OF THE METAMORPHIC ROCKS AND VEINS

The structural and petrologic relations of the serpentinite, serpentine veins, and talcose rocks of the ultramafic complexes indicate that they were formed by several distinct metamorphic processes, which have consistent sequential relations and consistent relations to the regional tectonic history. The contact-rock associations (steatite and blackwall; rodingite and serpentine-chlorite rock) display similar consistent relations.

Serpentinite

Pervasive serpentinization of dunite and peridotite to form both massive and schistose serpentinite took place early in the tectonic history of the complexes. The peripheral distribution of the sheared and schistose serpentinite, the general conformity of the schistosity of the serpentinite to the contacts of the complexes, and the distribution of shear polyhedra in the schistose serpentinite all suggest that the complexes were extensively serpentinized prior to emplacement. This conclusion is supported by the general lack of high-temperature contact-metamorphic effects in the country rock adjacent to the complexes. A logical and appealing interpretation of these relations is that serpentinization of the dunite and peridotite proceeded concomitantly with transport of the ultramafic rock by kneading of the solid mass through the country rock under tectonic stress, and that water for serpentinization was derived from the adjacent country rocks. Transport is considered to have taken place spasmodically, with intermittent periods of movement separated by periods of immobility. Shearing of the mass during periods of movement facilitated the entry of water and consequent serpentinization during intermittent periods of immobility, and serpentinization increased the mobility of the mass during subsequent periods of movement, primarily by dehydration of the serpentine under shear stress at high pressure and

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temperature, in the manner described by Raleigh and Paterson (1965, p. 3965) and by Reicker and Rooney (1966, p. 196). Serpentinization was not confined to the highly sheared marginal zones, but pervasively altered the adjacent un-sheared dunite and peridotite partly or entirely to massive serpentinite.

Serpentine Veins and Other Veins

Serpentine veins, including cross- and slip-fiber chrysotile asbestos and picrolite and their marginal alteration zones, were formed after emplacement of the ultramafic rocks, when tectonic transport and pervasive serpentinization of the rocks had ceased. In places, particularly in areas of complex younger folding near the Green Mountain anticlinorial axis, minor shearing after emplacement generated tension fractures in which chrysotile asbestos formed. Dunite, peridotite, and massive serpentinite yielded locally by frac-ture along local joint systems, but more com-monly along diversely oriented and somewhat irregular cracks; these became the loci of cross-fiber veins of chrysotile asbestos and picrolite. Sheared and schistose serpentinite yielded by slippage along shear surfaces, which generated innumerable tiny fracture openings; these be-came the loci of slip-fiber veins of chrysotile asbestos and picrolite.

In cross-fiber veins, including those in which the fiber axes are markedly oblique to the walls, irregularities along opposite walls match down to the finest details, demonstrating that the veins were formed by fracture filling with almost no replacement of the walls. Such evidence is lack-ing in the tiny slip-fiber veins, but presumably they formed under similar conditions.

The favored interpretation for the origin of the chrysotile asbestos and picrolite veins, based on the observed relations in northern Vermont, is as follows: In response to local stresses generated by minor regional shearing movements, tensional fractures were opened incrementally in the ultra-mafic rocks. In the massive serpentinite and dunite, the chief component of relative movement was normal to the fracture walls; in the sheared serpentinite, parallel to the walls. As the open-ings formed, diffusion of material from the walls and water from the fractures led to deposition of serpentine in the fractures and formation of the marginal alteration zones adjacent to the frac-tures. Where the rate of deposition in the veins equalled the rate of opening of the fractures, chrysotile asbestos was formed, with the fiber axes parallel to the direction of relative move-ment of the opposite walls. Where the rate of

opening appreciably exceeded the rate of deposi-tion, picrolite was formed, with the coarse fibers and columns poorly oriented.

Magnetite, calcite, and brucite formed essen-tially contemporaneously with the serpentine veins and under the same conditions. They record the concentration and local movement of material that could not be accommodated in the serpentine minerals.

Talcose Rocks and the Steatite-Blackwall Association

A sequential association is clearly demon-strated by the invariable replacement relation and the peripheral distribution of talcose rocks with respect to serpentinite, along with the pseudo-morphic relation of talc to cross-fiber chrysotile asbestos. The temporal separateness of serpen-tinization and steatitization is less evident. The inference of separateness rests upon the fact that the extent of serpentinization is unrelated to the width of the talc-carbonate rock zone and that serpentinite is strongly affected by the younger folds, whereas steatite and talc-carbonate are affected only weakly or not at all. On these bases, steatitization is inferred to be the latest meta-morphic episode in the geologic history of the ultramafic rocks. Though of essentially simul-taneous origin, talc-carbonate rock (and car-bonate-quartz rock) and steatite were formed by very different and essentially unrelated meta-morphic reactions. The consistent relation between the width of the talc-carbonate rock zone and that of the steatite zone suggests that the talc-car-bonate rock reaction triggered or facilitated the steatite-blackwall reaction by the release of water during the alteration of serpentinite to talc-carbonate rock.

Available evidence indicates essentially con-stant-volume replacement relations. Comparison of rock compositions then indicates that the alter-ation of serpentinite to talc-carbonate rock was primarily due to carbon dioxide metasomatism. The fundamental processes were addition of CO_2 and loss of H_2O; additions and losses of other components were negligible. Loss of water to the adjacent country rock may have triggered or facilitated the steatite-blackwall reaction (see Chidester, 1962, p. 89ff. for supporting analytical data).

The distribution of carbonate-talc-quartz rock and carbonate-quartz rock appears to be con-trolled by zones of faulting or intense shearing, which would furnish ready access for CO_2. These rocks appear to represent intermediate and end

stages in the process of carbon dioxide meta-somatism.

The replacement of albite porphyroblasts and other metamorphic minerals of the country rock by the chlorite and biotite of the blackwall demonstrates that the blackwall formed during or after the peak of regional metamorphism. The age equivalence of the blackwall and steatite are indicated by the fact that neither is cut by the other and by the generally sympathetic relation between the width of the two zones. Their genetic relation is further indicated by the following petrologic considerations.

As in the case of the talc-carbonate rock reaction, evidence for constant-volume replacement is the basis for determining the steatite-blackwall reaction. On this basis, comparison of the compositions of serpentinite, steatite, blackwall, and country rock demonstrates that the reaction was essentially one of interchange of constituents between serpentinite and schist, leading to a zoned distribution of steatite and blackwall between serpentinite (or talc-magnesite rock) and country rock. The reaction chiefly involved loss of Mg and H_2O from the serpentinite to the blackwall zone and loss of Si from the country rock to the steatite zone. Where the adjacent country rock was amphibolite or carbonate rock, and hence low in Si, the reaction was repressed and the steatite and blackwall zones were poorly developed.

As the steatite-blackwall reaction progressed, both the steatite and blackwall zones widened, chiefly at the expense of serpentinite (or talc-magnesite rock) and country rock, respectively. The inner margin of the blackwall zone also altered slowly to talc, so that the outer part of the steatite zone is derived from the country rock.

Other reactions in areas of low-grade metamorphism were minor, but in albitic schists Na was displaced outward at the advancing blackwall-schist boundary to form striking concentrations of albite porphyroblasts; where the schist was graphitic, graphite also was displaced outward. In areas of higher grade metamorphism, the activities of mobile components critical to the formation of chlorite and biotite attained such values that chlorite and biotite were concentrated in successive zones outward from the steatite zone. Where the wallrock was amphibolite, Ca migrated into the steatite zone to form a marginal shell of tremolite.

Serpentine-Chlorite Rock and Rodingite

The absence of contact rocks of the serpentine-chlorite rock and rodingite association in most ultramafic rock complexes suggests that the rocks of this association were formed under unusual conditions. The presence, in identical country rock, of serpentine-chlorite rock and rodingite within a few feet of blackwall and steatite indicates that the two associations must have been formed during different metamorphic episodes, and therefore presumably under different physical conditions. The fact that serpentine-chlorite rock and rodingite occur only adjacent to serpentinite, at contacts where talcose rocks are absent, suggests that such contact rocks are older than steatite and blackwall, and probably are related to the emplacement of the ultramafic rocks. The association of serpentine-chlorite rock and rodingite exclusively with large ultramafic complexes that contain masses of relatively fresh dunite and peridotite suggests that such bodies of rock were appreciably hotter during emplacement than the other bodies of ultramafic rock. The narrowness of the rodingite zone indicates, however, that the ultramafic rocks were not much hotter than the surrounding country rock. The cumulative evidence is that the serpentine-chlorite rock and rodingite were formed under rather special conditions of contact metamorphism.

The replacement relations of rodingite to country rock and of serpentine-chlorite rock to rodingite are sequential. These relations permit, but do not require, that the replacements represent a single complex reaction. The local projection of tongues of serpentine-chlorite rock along fractures beyond the rodingite zone suggests the possibility that the serpentine-chlorite reaction was separated from the rodingite reaction by a discrete time interval, and thus took place at a lower temperature.

Rodingite was formed by alteration and replacement of the country-rock minerals chiefly by diopside, garnet, vesuvianite, and clinozoisite. Two stages are distinguishable: (1) alteration to diopside, clinozoisite, and garnet, and (2) replacement of these minerals by a more calcic garnet and vesuvianite. These relations, together with the differences in mineralogy that reflect differences in protoliths and composition of adjacent beds, indicate that the rodingite reaction involved only relatively minor migration of components, and that the successive mineral reactions record the effects of changes in temperature and, probably, the activities of volatile constituents.

The uniform character of the serpentine-chlorite rock and the zonal distribution of serpentine and chlorite, grading from predominantly serpentine at the contact with serpentinite to pre-

dominantly chlorite at the contact with rodingite, demonstrate that the serpentine-chlorite rock reaction was metasomatic, involving wholesale conversion of rodingite progressively to chlorite and serpentine, chiefly by addition of H_2O and of Mg from the ultramafic body.

The foregoing relations and conclusions suggest the following interpretation for the origin of the rodingite and serpentine-chlorite rock assemblage:

A large body of ultramafic rock containing considerable amounts of dunite and peridotite reached its present site at temperatures significantly, but not greatly, above those of the surrounding country rock. The emplacement temperature of a body was a function of its size and its distance of transport from the site of accumulation. Because the mass of ultramafic rock was slightly hotter than the surrounding terrane, the country rocks were contact metamorphosed in a thin zone adjacent to the ultramafic rocks.

The mineral assemblages characteristic of the rodingite are seemingly of abnormally high grade partly because dunite and peridotite in the mass behaved essentially as sinks for water, thereby lowering the activity of water in the country rock and lowering the temperature of formation of the mineral assemblages characteristic of the rodingite. The dehydration of serpentine under shearing stress at high pressures and moderate temperatures, advanced above (see p. 350–351) as a major factor in facilitating tectonic transport of the mass, suggests a second factor that may have been effective, perhaps even dominant, in lowering the activity of water in the country rock immediately adjacent to the ultramafic rocks: At sufficiently high temperatures, sheared serpentinite in such a tectonically transported mass would be markedly water-deficient when the mass came to rest and would be a very effective sink for water from the adjacent country rock.

As hydration of the ultramafic rocks proceeded, the activity of water in the ultramafic rock and the immediately adjacent country rock slowly rose and the temperature decreased. When the rising water pressure and falling temperature reached critical values, rodingite became unstable in contact with serpentinite. The two rocks then reacted to form a narrow zone of serpentine-chlorite rock, which enlarged by encroachment upon the bordering rodingite. The advancing wave of alteration, dependent upon the addition of Mg derived from the serpentinite, was characterized by formation of chlorite next to the rodingite. As the wave of alteration advanced

farther, early-formed chlorite was altered progressively to serpentine.

The interpretation outlined above suggests that rodingite and serpentine-chlorite rock were probably formed sequentially in a narrow time interval, that this interval coincided with that in which the asbestos and other serpentine veins were formed, and that the physical conditions conducive to the formation of one were also conducive to formation of the other.

ROLE OF THE TECTONIC AND SEDIMENTOLOGICAL ENVIRONMENT

The relation of size and character of the ultramafic complexes to their tectonic and metamorphic setting, considered in the context of genetic concepts outlined in the foregoing sections, illuminates the role that the tectonic history and sedimentological environment played in the development of the complexes.

The structural relations of the contacts and septa of the complexes demonstrate that the ultramafic rocks were emplaced by forceful intrusion. The structural history and the concepts advanced for derivation and emplacement of the ultramafic rocks lead to the conclusion that the stage of igneous derivation occurred during or near the end of the eugeosynclinal deposition. Eugeosynclinal deposition in this belt ended with the disturbance that produced the early folds and that culminated in the unconformity at the base of the Silurian section. Tectonic stresses generated during this disturbance mobilized the ultramafic igneous rocks and kneaded them through the overlying water-saturated sediments. At successive positions the transported ultramafic rocks successively encountered more extensively folded country rock, so that emplacement of the ultramafic rocks at their present positions essentially post-dated the early folds. Stratigraphic relations indicate that exposed complexes were emplaced at considerable depths. Under such conditions, in a thick water-saturated geosynclinal pile, small or far-travelled bodies would be extensively serpentinized and would be finally emplaced at temperatures near those of the enclosing rocks; large or short-travelled bodies would be less extensively serpentinized, and would be emplaced at higher temperatures. Thus the family of characteristics displayed by the complexes appears to depend significantly on the tectonic and sedimentological environment, and is related to the size of the mass of ultramafic rock, the distance that the mass has travelled through wet sediments, and the local erosional pattern.

354   CHAPTER 26

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SECTION II

Origin of the Ludlow Quadrangle Ultramafic Bodies

1.   Introduction

The ultramafic rocks of the Ludlow area are a portion of a long, discontinuous belt of ultramafic and related igneous rocks which begins in Western Newfoundland, extends through New Brunswick and Gaspé and turns south through the state of Vermont. Ultramafic rocks similar to these continue far south into the southern states, but since there is a large discontinuity between these and the Vermont ultramafics, this section will be restricted to the Vermont-Newfoundland zone and its implications for ore distribution in the Ludlow area.

The ultramafic bodies near Ludlow, Vermont lie directly on the trend of the main ultramafic zone. These bodies have proven to be of ultramafic igneous origin by the presence of undoubted igneous rocks such as dunite, harzburgite and gabbro in or near some of the larger bodies. These early igneous rocks have been metamorphosed to serpentinite and talc rocks with various amounts of Mg or Fe carbonates as additional products of reaction. For a precise discussion of the petrology and field relations the reader is referred to Section III.

2.   Emplacement of Ultramafic Rocks

The geologic history of the Ludlow area may be roughly

summarized as follows. Paleozoic history begins with early (late Precambrian to Ordovician) buildup of a continental shelf on the eastern edge of the Green Mountains; where eugeosynclinal (deep shelf) sediments are deposited. These sediments would consist of a lower sequence of continental clastics followed quickly by shallow marine carbonates and then deeper water sandstones and shales as the edge of the continent subsides. The depositional environment would be similar to the presently building Atlantic continental margin where a sequence of up to 15 km of similar sediment is being deposited. One must recognize that a substantial amount of ocean basin must have existed to the East of this older continental margin.

On the opposite side of this ocean basin lay a similarly developing continental margin bordering lands which would soon become part of North America. In addition to the two continents and the intervening ocean basin it is likely that a large number of volcanic islands and perhaps a series of island arcs similar to Japan may have existed in the ocean basin. The sediments deposited during this time are now visible as the Vermont Valley sequence of schists and phylites in which the talc ore bodies are enclosed.

During the later history of the continental margin, an oceanic trench developed on or near one of the continental margins. The trench became the site of subduction and consummation of the oceanic "plate" which consisted primarily

24

of basaltic, gabbroic and ultramafic rocks. The destruction and slow closing of the ocean eventually brought the two continental land masses into collision and the two continents were welded along a "suture" zone which is today represented approximately by the ultramafic zone. During this collision the sediments were deformed and metamorphosed by the heat and pressure evolved. The oceanic plate was, for the most part, consumed in the trench which lay between the continents and was reabsorbed in the earth's mantle. However, the intense stresses involved in these tectonic events caused parts of the oceanic crust to be thrust upwards into the overlying sediments as enormous thrust sheets of ultramafic and gabbroic rocks probably before the main collision occurred. In the Vermont region the tectonism was so strong that the remnants of the old ocean basin are dismembered and extremely deformed. In Newfoundland, however, enormous sections of the old ocean are virtually intact, as if an entire section of the 6 km thick ocean crust had been gently thrust upon the sediment pile. The section is so complete that it has been used as a model to determine what the nature of the present oceanic crust is, based upon seismic data. The section starts with a thin layer of pillow basalts, indicating undersea eruptions, followed by a "sheeted dike complex" composed of a packed mass of vertical "feeder" dikes up to 2 km thick, next is a layer of deeper, homogeneous gabbro which may possibly have been the site of a progressing chamber of magma. At the base of the gabbro are so-called layered gabbros showing cross-
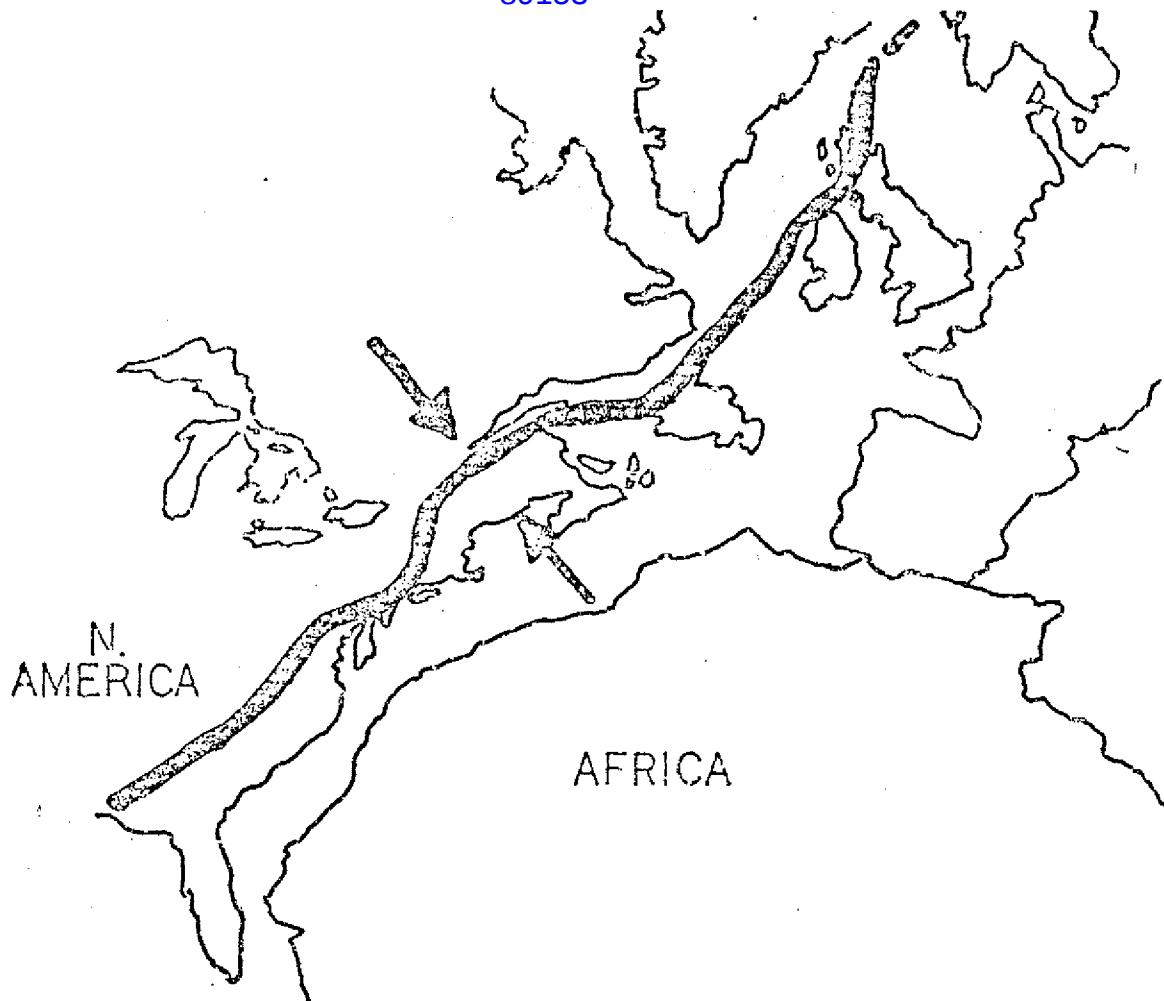
Figure 2 - Ordovician continental collision responsible for emplacement
of ultramafic and mafic slivers of oceanic crust (ophiolites). Heavy
line approximates collision line or "suture". In addition to all
Eastern North American ophiolites, Newfoundland and Scottish (Shetland)
ophiolites are on this zone. Below are sketches showing collision.
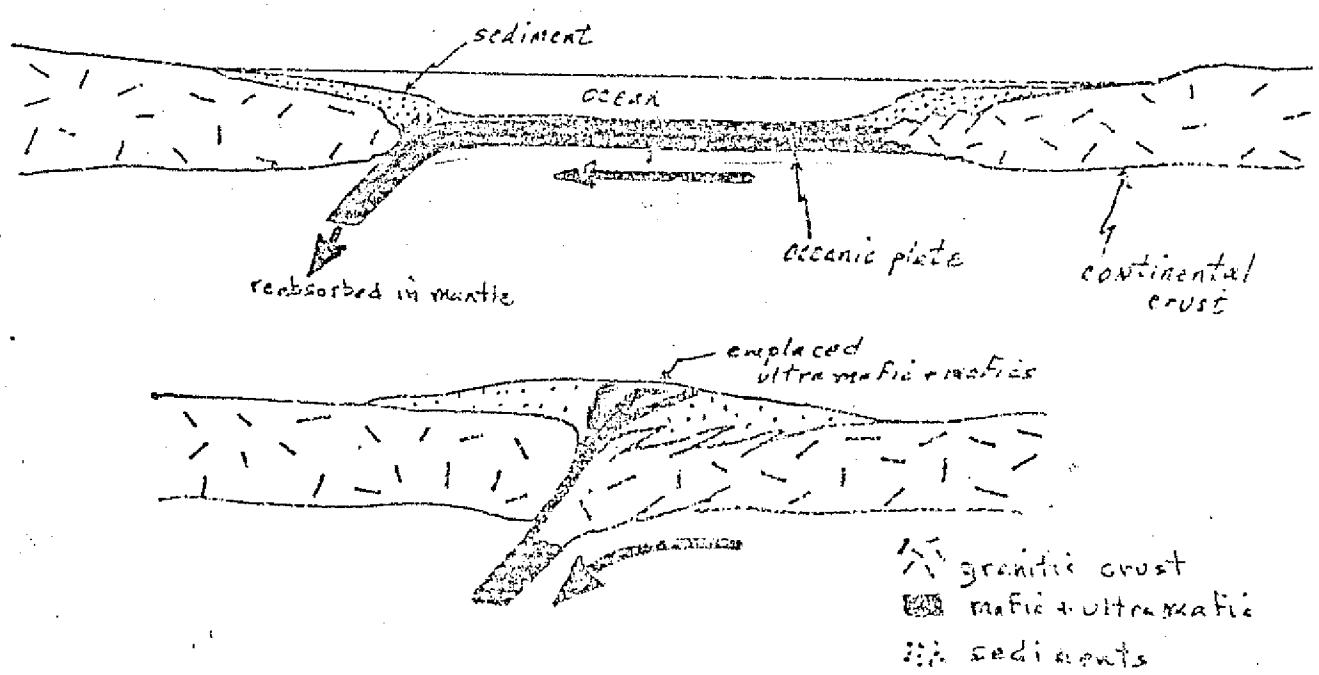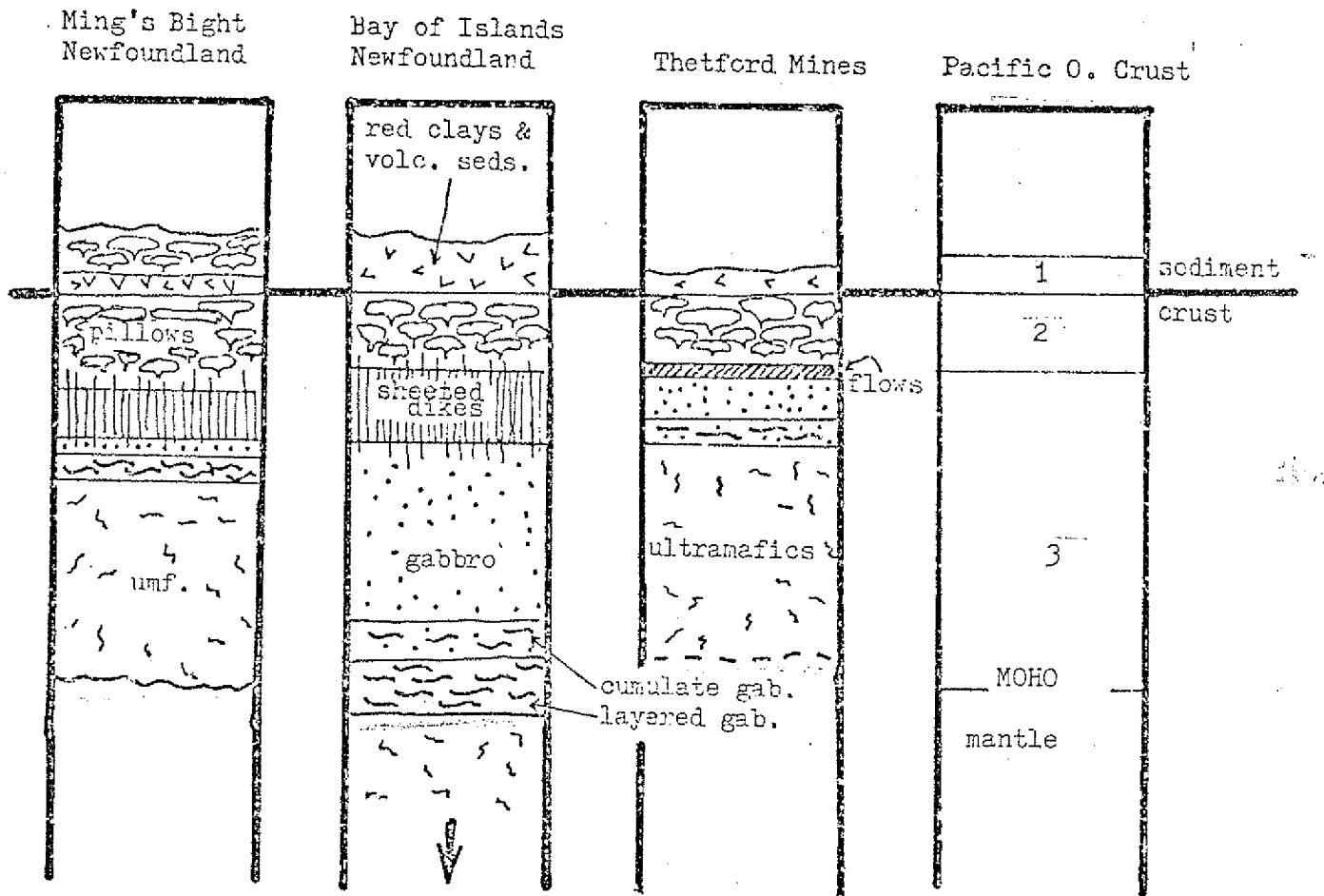
Figure 3 - Generalized cross-sections of important mafic and
ultramafic rock sequences in North America as compared to
the seismicly determined rock units of the Pacific Oceanic
Crust.Layer 1 of the Pacific is predominantly sediment, Layer 2
has been drilled and usually consists of pillow basalt and
flows at the top. Layer three is of unknown composition but its
properties suggest compositions similar to gabbroic and ultra-
mafic rocks. The "ophiolite" sections found on our continent
therefore, appear to be various types of thrust-fault emplaced
sections of oceanic crust. Dismembered stringers and zones of
ultramafic rocks such as those in the Ludlow area are highly
deformed equivalents of parts of these sequences.

27

bedding, cumulate banding and other textures indicative
of crystal setting at the bottom of a large magma chamber.
The final sequence of this 6-7 km thick section consists of
ultramafic rocks and serpentinites, some of which may be
actual pieces of the upper mantle. Throughout the rest of
the zone various pieces of this sequence can be found, but
only rarely in such good condition. The Thetford "ophiolites",
as such a sequence is referred to, is similar but not as com-
plete. The rocks of Vermont seem to be confined chiefly to
the lower rocks of the sequence (gabbros and ultramafics).
The reason for this is not known. The granitic rocks found
at the Rainbow Quarry are also known to occur in the New-
foundland sequence and are often similarly depleted in
potassium (lack of orthoclase feldspar). These rocks are
discussed in detail in Section III. It should be mentioned
that in addition to so-called "ocean crust" rocks, other
geologic sources may also provide thrust slices of mafic or
ultramafic composition. These geologic zones are island arcs,
oceanic islands and fracture zones. All of these may be
separated from the oceanic crust and thrust into the over-
lying sediments, and many modern examples of these have been
documented.

All of the emplacements of mafic and ultramafic rocks
discussed so far involve more or less solid tectonic trans-
port. During these tectonic events liquid injection of mafic
dikes may also occur but ultramafic dikes are not known.
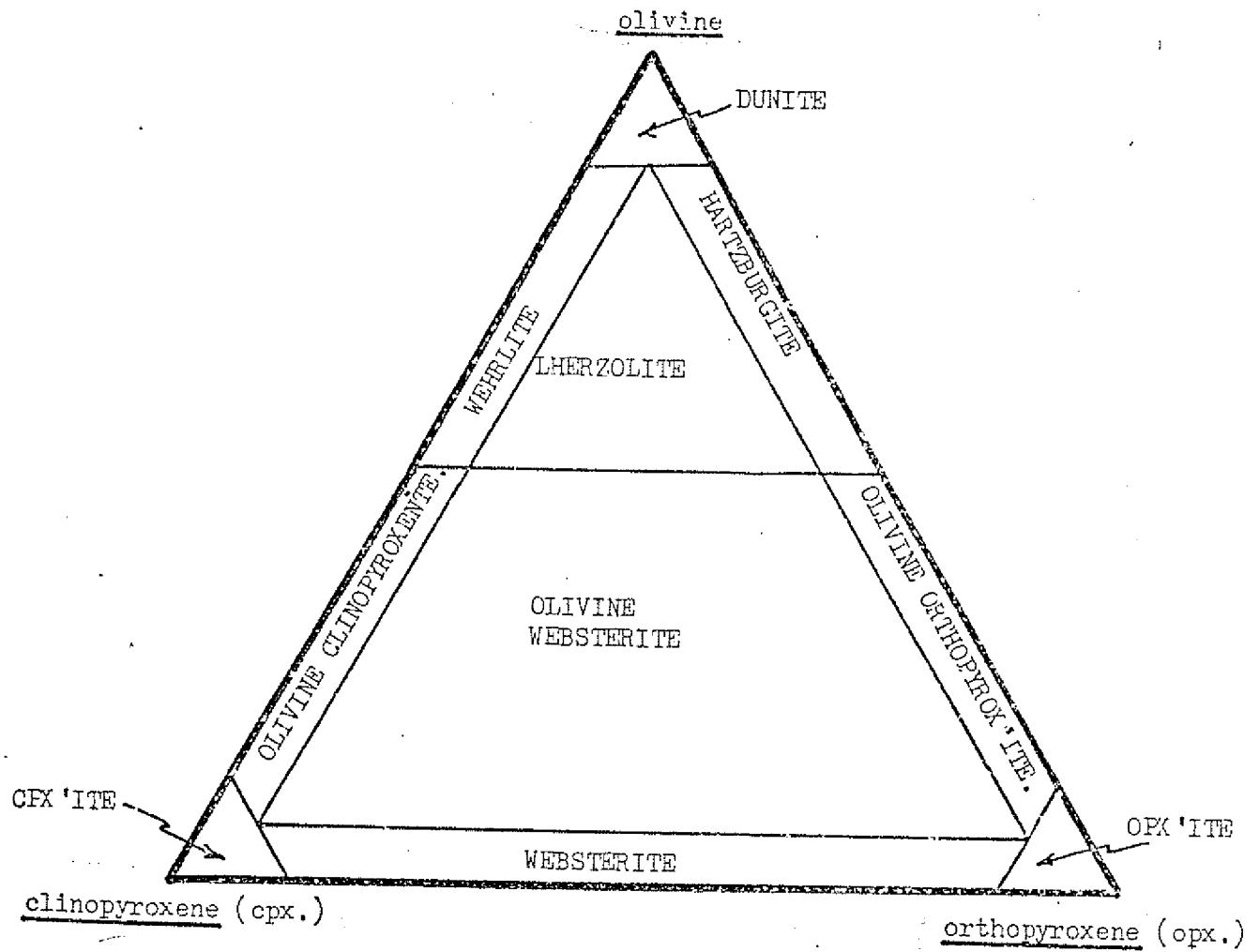
Figure 4 – Classification of ultramafic rocks based on relative
amounts of olivine, orthopyroxene, and clinopyroxene at each
corner of the triangular plot. For example Dunite is 90 to
100% olivine; Wehrlite is 50 to 90% olivine with the remaining
portion nearly all clinopyroxene. These rocks all alter to
serpentinites as well as other products. If partly altered the
terms "serpentinized harzburgite" and "serpentinized dunite"
and so forth may be used.

Thus, some of the chlorite cinders are thought to be early mafic (basaltic) dikes injected into the ultramafic zone prior to, during or after the thrust fault emplacement. The basalt dikes would later be metamorphosed to greenschist facies chlorite schists.

The metamorphism of the serpentinites and ultramafic rocks to talc schists or chloritic rocks probably occurred during the emplacement of the ultramafics.

3. Metamorphism and Deformation of the Ultramafic Zone

The emplacement of ultramafics in the marginal sediments near the site of oceanic plate destruction was followed by the collision of a continental land mass with North America. During this time the entire sequence of sediment and ultramafic sheets was deformed again, probably producing the Chester Dome as well as a numerous regionally important folds. The distribution of the ultramafics around the dome probably reflects the fold geometry of a single ultramafic zone. Although the bodies of ultramafics are very discontinuous around the Chester Dome hinge, they lie at the same lithologic level as the more continuous Ludlow area bodies. More detailed field work will undoubtedly result in the discovery of more ultramafics to the east and west of Hammondsville, but these bodies may have little or no surface expression, thus accounting for the few reports in this well explored terrain. Recent mapping on Keyes Mountain (Nisbet, 1976) has shown the persistence of a layer of amphibolitic rocks which appear to

be closely associated with the ultramafic zone; lying in the footwall. Future exploration might employ this marker unit. These amphibolites are well known in the footwall of the Ludlow area bodies.

4. Emplacement of Basalt Dikes

The last important tectonic event to occur was the rifting apart of the two "welded" continents during Mesozoic time ($\approx$185 m.y.a.). The line of separation did not coincide with the older line of welding (the ultramafic zone), but instead lay to the east and marks the present continental margin.

During the early stages of this separation an unsuccessful attempt was made to split the continents up the Connecticut River Valley. This resulted in the Triassic graben and volcanic flows and sills in Massachusetts and Connecticut and in the volcanic centers to the north, for example, Mount Ascutney and Little Ascutney. The basalt dikes intruded into the Hammondsville body as well as those intruded into the Gassetts schist are probably related to this event.

Volcanicity ceased, however, when the rift failed to continue and a new rift form further to the east along the present continental margin.

The emplacement of basalt dikes is the last significant event to occur in the Hammondsville ore body.

5. Timing of Ultramafic Emplacement in the Northeast

Table II is a synopsis of geologic events through time
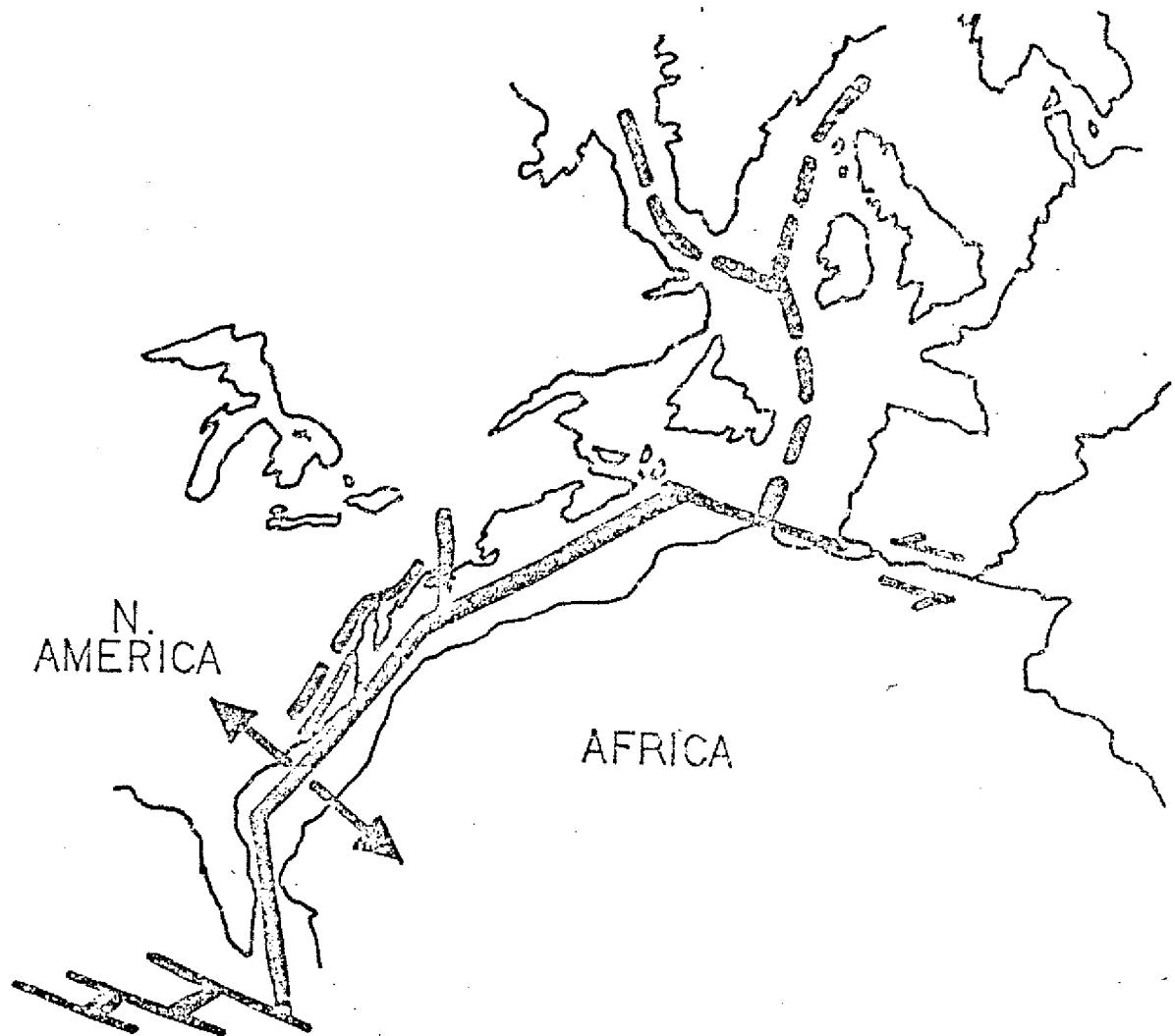
Figure 5 - Breakup of Africa, North America and Europe, during the Mesozoic
at about 185 million years ago. Heavy lines are rift zones. Short lines
in   in North Atlantic represent delayed rifting; in N. America represent
early rifts that failed to open (ex. Connecticut River & New Jersey lava
flows and graben in Triassic). Sketches below. Failed openings look like (1).
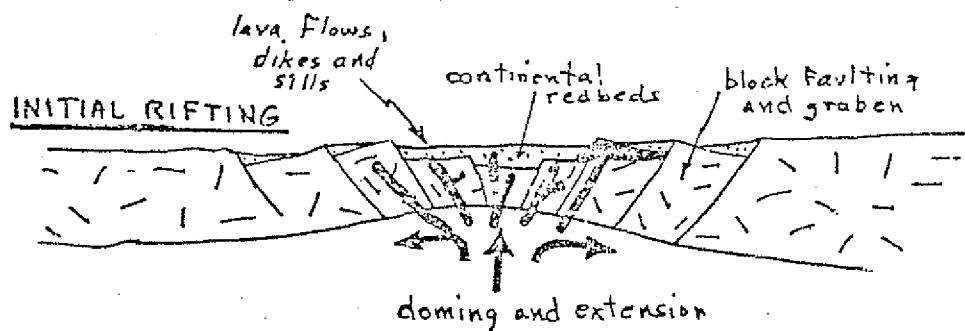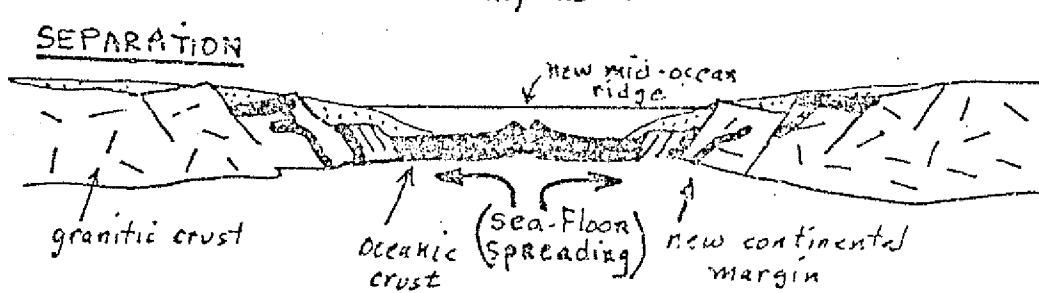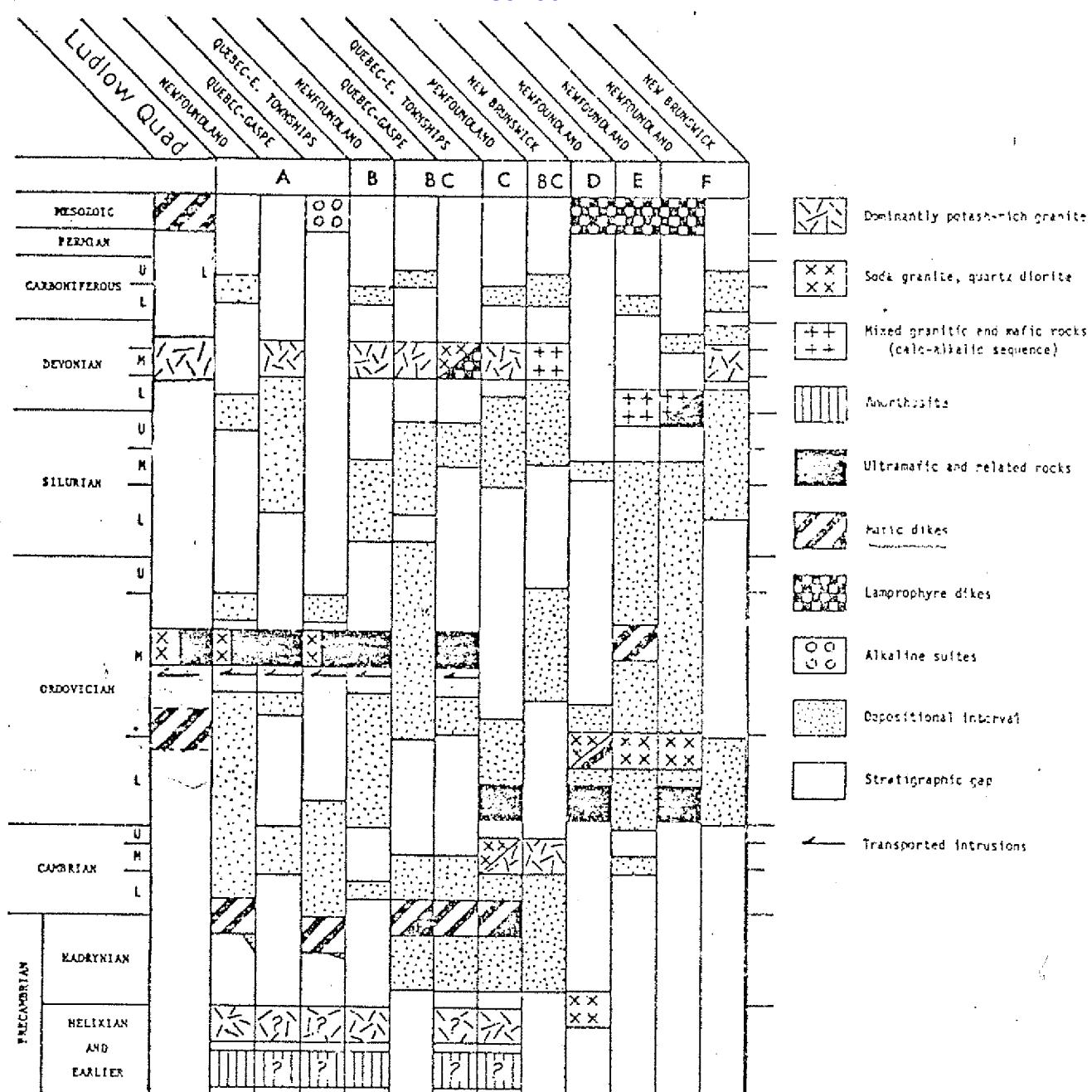
Table II – Timing of the ultramafic and mafic emplacement events of the
Ludlow Quadrangle in relationship to the Quebec-Gaspe and Newfoundland
ophiolites. Black represents talc schists, serpentine or chloritic
core rocks and associated ultramafics in all of our presently worked
orebodies. Rainbow granite may correlate to possible mid-Devonian
event as well as well as original emplacement. Basalt at Hammonds-
ville is probably related to Mesozoic rifting events associated with
the opening of the present Atlantic Ocean.

from Vermont to Newfoundland. The letters A through I represent specific localities in the different areas and need not be discussed in detail. The first column indicates the possible timing relationships for Ludlow Quadrangle ultramafic rocks. Ultramafic emplacement in Middle Ordovician time may have been preceded by mafic dikes. These dikes are now metamorphosed and are represented by the amphibolites which have been previously discussed in association with the ultramafic zone. The emplacement of ultramafics was matched to the Quebec, Gaspe and major Newfoundland emplacements although some ultramafics may have been thrust into the sediments in lower Ordovician.

The timing of the granitic rocks (tonalites and trondjhemites at Rainbow Quarry) is uncertain. They may have come in with the ultramafic bodies originally as in Newfoundland, or they may be representative of the Mid-Devonian igneous event. Mafic dike emplacement is shown as Mesozoic.

6. Stratigraphic Correlations with Ultramafic Rocks

The Vermont Valley sequence of metamorphosed sediments is bounded in the Ludlow area by the Precambrian front at Okemo Mountain to the west and the Precambrian core of the Chester Dome. Previous workers have considered the sequence to be essentially undisturbed stratigraphy on the regional scale; but increasingly detailed recent work has established that the sequence has been greatly disturbed and that most of the contacts between various formations are tectonic

(faulted) contacts. This correlates well with the modern concepts of near-trench deformation of marginal sedimentary wedges during the consumption of an ocean basin. This is so because the sediments are being stacked and telescoped as thrust sheets in the same manner as the ultramafics. The final sediment pile, which would be elevated during the eventual collision, would consist of a fault-stacking that would closely resemble a normal sedimentary sequence. This is apparently the case for the Vermont Valley Sequence. The sediment thrust sheets may contain one or more lithologic units of very great strike length, since the process of thrusting is occurring over long (1,000's of km) zones. it is to be expected that some regularity of order may be established in the stacking of the sheets. Therefore, the ultramafic sheet may always be confined to a relatively narrow zone; but may be able to cross "apparent" formational boundaries. For example, the zone may lie on the Moretown/Cram Hill contact in the Ludlow area but may cross into other units along strike. All of this depends on the particular variations in thrusting mechanics along the old continental margins.

In summary, exploration may be tied to lithologic boundaries as we have done in the Ludlow area. It must be recognized that these boundaries are probably old thrust surfaces (details such as mylonitization or fault gauge may not survive metamorphism and deformation). One must be prepared

for the eventualities that:

    1) there may be multiple zones paralleling each other along a narrow strip.

    2) any given zone of ultramafics could cross an apparent "Formational" boundary at some point.

It is obvious that the employment of the "Formation" and "member" terms to these rocks is a misuse of stratigraphic nomenclature; since the details of time relationships and early sedimentological sequence have been lost.
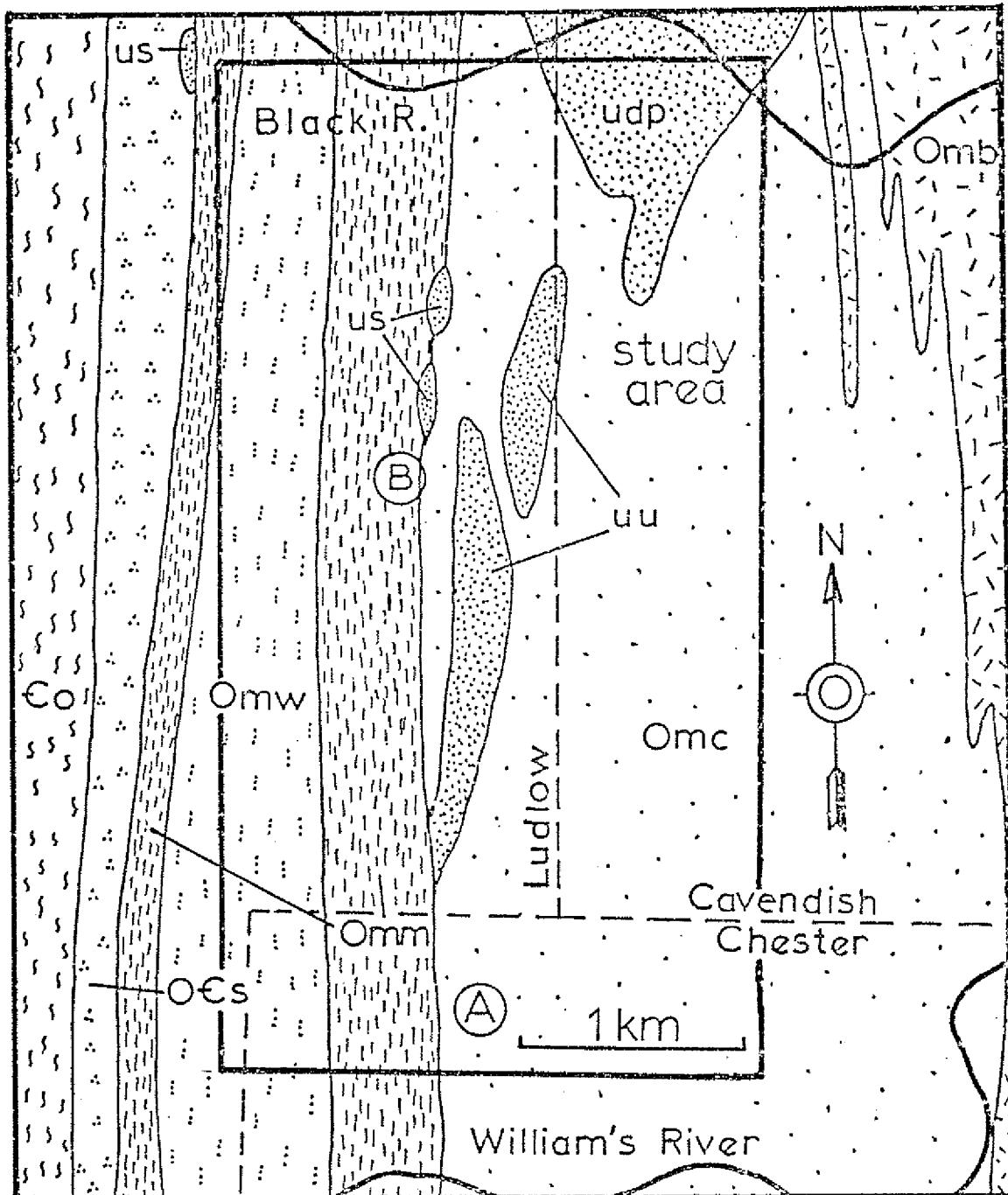
Figure 7 - Geologic setting of study area showing geology as mapped by Thompson (1950). Area "A" is referenced in text as the vicinity of the Cram Hill quartzite horizon; area "B" is subarea B in text.

Missisquoi Formation:

Omc = Cram Hill member	OCs = Stowe Formation
Omb = Barnard Volcanic member	Co = Ottauquechee Formation
Omm = Moretown member	uu = undifferentiated ultramafics
Omw = Whetstone Hill member	udp = dunite, peridotite, serpentinite
	us = serpentinite, carbonate rock, talc-carbonate rock & steatite
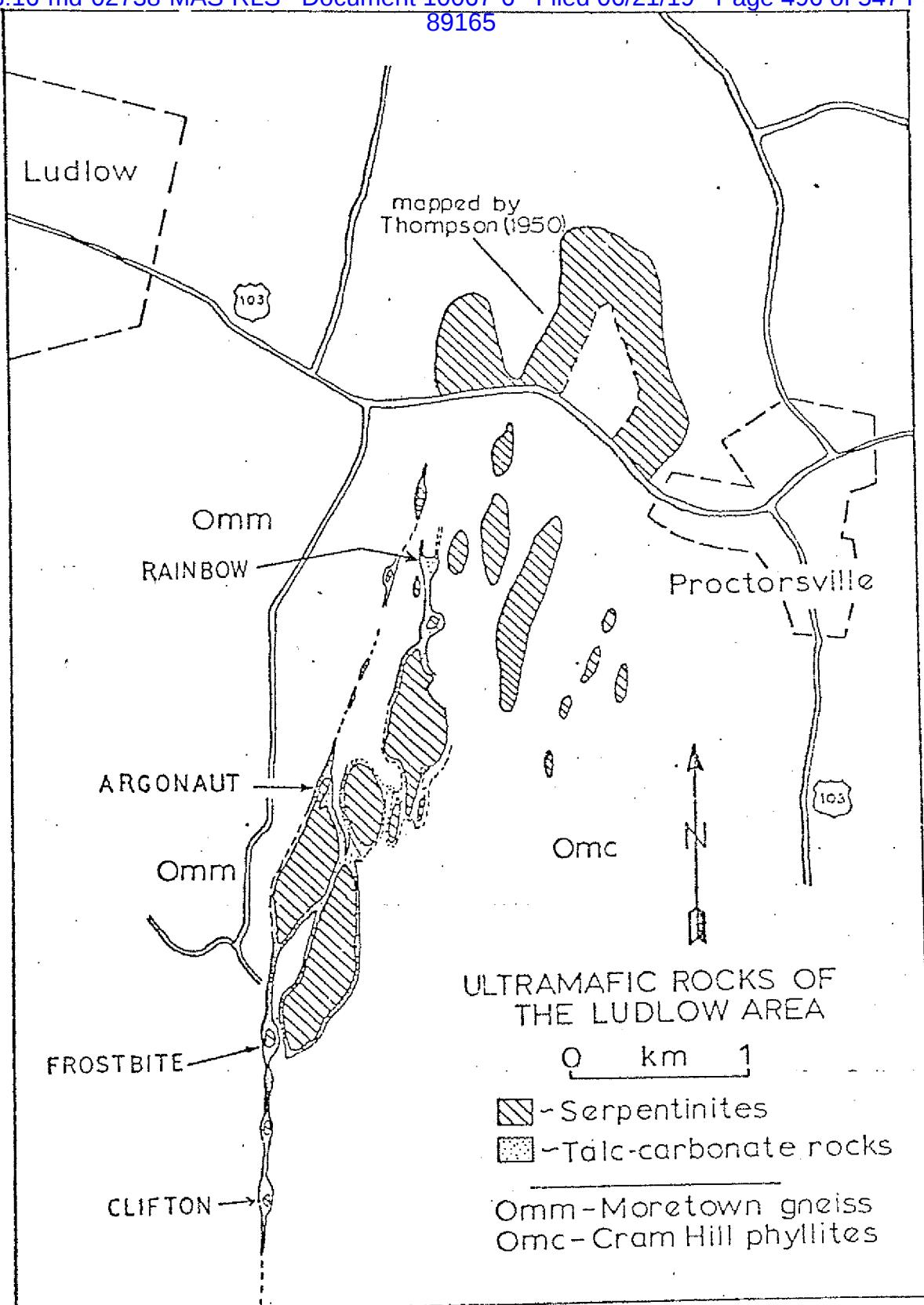
Figure 8

Exhibit 30

TRICLINIC TALC AND ASSOCIATED AMPHIBOLES FROM GOUVERNEUR MINING DISTRICT, NEW YORK[1]

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ABSTRACT

New chemical, optical, and X-ray data are given for talc, tremolite, and a manganoan amphibole (tirodite) from the Gouverneur mining district, New York. All talc examined is found to be triclinic, $a = 5.25_5$, $b = 9.13_7$, $c = 9.44_8$ Å, $\alpha = 90°46'$, $\beta = 98°55'$, $\gamma = 90°0'$, space group $C1$ or $C\bar{1}$, structure type 1-layer triclinic (1Tc). Chemical analysis gives the composition of talc from the Arnold pit as $Mg_{3.04}Si_{3.96}O_{10}F_{0.10}(OH)_{1.90}$. On the basis of fluorine analyses of 22 talcs from worldwide localities it is observed that talc derived from metamorphosed sedimentary rocks contains appreciable fluorine, from 0.11 to 0.48 weight percent, whereas talc derived from ultramafic rocks contains less fluorine.

Two of the three tremolite specimens examined have prominent lamellae, oriented parallel to $(10\bar{1})$, of a second amphibole having the following unit-cell parameters: monoclinic, $a = 9.50$, $b = 18.04$, $c = 5.28$ Å, $\beta = 102°25'$, space group $P2_1$ or $P2_1/m$. Chemical and X-ray evidence indicates that this amphibole is tirodite having the approximate composition $Ca_{0.2}Mn_{0.9}Mg_{5.9}Si_8O_{22}(OH,F)_2$. The tirodite probably exsolved from the host tremolite at temperatures below 500°C.

New unit-cell data are given from three tremolites. X-ray powder data are given for talc and tremolite.

INTRODUCTION

The purpose of this paper is to present new chemical, X-ray, and optical data for talc and the associated amphiboles tremolite and tirodite found in certain schists from the Gouverneur mining district, New York. This study is part of a broader investigation which the authors are conducting on the physical and chemical properties of talc and the associated minerals lying in the system $CaO\text{-}MgO\text{-}SiO_2\text{-}H_2O\text{-}CO_2$. The metamorphosed sedimentary rocks of the New York Grenville Lowlands are ideal for such a study for many of the mineral compositions lie mostly within this system. The present paper will present data only for the talc-tremolite schists of the Gouverneur area. Although the chemical and physical properties of talc and tremolite were thought to be well known, our study and the recent studies of Bown (1966) and Rayner and Brown (1966) show that much is yet to be done in order to fully characterize these phases.

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[1] Studies of silicate minerals (10). Publication authorized by the Director, U. S. Geological Survey.

THE GOUVERNEUR MINING DISTRICT

The Gouverneur, or Balmat-Edwards, mining district is in the Grenville Lowlands of the northwest Adirondacks, St. Lawrence County, New York. Most of the bedrock of the Gouverneur area consists of metasedimentary and metasomatic rocks referred to as the Precambrian Grenville Series. The talc containing schists are found in a northeast trending belt which was described by Engel (1962) as more than six miles long, dipping approximately 45° to the northwest probably extending down dip some 2,500 feet, and attaining a maximum thickness of greater than 400 feet. The talc bodies occur as sheets and lenses in a highly folded and sheared marble of the Grenville Series.

Metamorphic reactions between quartzite and dolomite produced various magnesium- and calcium-bearing silicates, especially diopside, tremolite, anthophyllite, and talc. Some of the talc and anthophyllite and probably all the serpentine formed by later alteration of tremolite. Some of the schists are calcitic, probably as a by-product in the alteration of tremolite to a more magnesium rich phase.

The amounts of the various minerals differ throughout the area; however, the predominant mineral is usually tremolite. In addition to the pyroxene, amphibole, talc, and serpentine constituents of the ores, there are also varying amounts of quartz, carbonates, gypsum, chlorite, and accessory minerals. Texturally the talcs range from massive to platy, and they vary in color from buff and gray to white.

OCCURRENCE

The Arnold pit of the International Talc Company, near Fowler, was visited in 1961 and again in October, 1966. Many of the samples described in this study were obtained from this pit.

The exposed rock at the Arnold pit, near the old Arnold shaft, consisted of a glaciated surface which was being cleared of soil, and into which excavations were being made. The width of the exposure was estimated to be from about 280 to over 300 feet in the area sampled. The sequence of rock types from the footwall dolomite to the hanging wall dolomite was observed to be as follows, as traversed across the floor of the mine in a westerly to northwesterly direction:

(1) footwall dolomite
(2) "limy talc" rock, about 30 feet (G-16)
(3) "coarsely crystalline talc" lens, about 5 feet (G-17)
(4) massive "talc ore," about 115 feet (G-18)
(5) a sequence of an irregular interbedding of coarsely crystalline

tremolite (variety hexagonite) and massive talc ore, about 130 to 150 feet (G-19, 20, 21, 22)

(6) hanging wall dolomite.

The occurrence of a lens of coarsely crystalline talc near the footwall was atypical of the exposed rock. The complex interbedding of coarsely crystalline talc and the hexagonite-bearing rock was pronounced toward the hanging wall. The exposures of this type of talc ranged from a few inches to a few feet in width. The specimens of the coarsely crystalline talc which were collected for mineralogical study were found to be dominantly talc with a small amount of clear unaltered tremolite. The relatively coarse grained talc, known as "scale" at the mines, is associated with but distinctly different from the fine-grained commercial talc.

A similar coarsely crystalline talc was noted in May, 1961, on the fourth level of the Wight mine of the International Talc Company, which is located about 3,000 feet to the southwest of the Arnold pit, in the same formation. The material from this part of the mine is richer in tremolite; the translucent to pure white talc and clear colorless tremolite being the major phases. Minor fibrous anthophyllite, partly altered to talc, is also present as a minor constituent. The sheetlike body of tremolite-coarsely
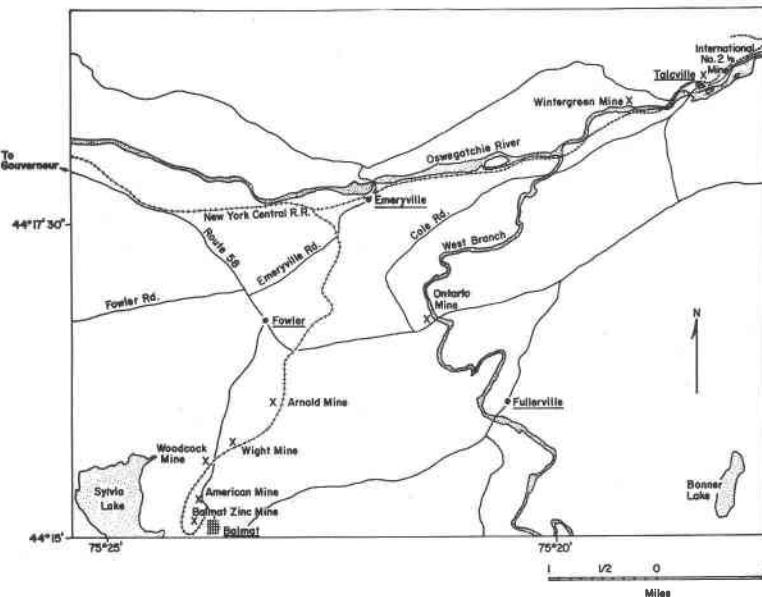
Fig. 1. Index map of the Gouverneur talc mining areas, St. Lawrence County, New York. Modified, in part, from Engel, 1962, Plate I.

crystalline talc rock was about 12 feet thick where examined and was reported to extend more or less continuously along the strike of the ore. The body extends from the surface or near the surface down through the sixth level of the mine.

Additional samples of well crystallized talc obtained previously from the Arnold pit (G-1), and the "Talc" mine (CS-1), Gouverneur, N.Y., and also a sample of nearly pure quartz-tremolite rock from an area 3/4 of a mile southwest of the Wight mine (G-24) were also studied. The location of the various mines is given in the index map (Figure 1).

The apparent mineral associations of the more carefully studied samples are as follows:

(1) G-1, talc-minor clear tremolite and anthophyllite

(2) G-16, clear tremolite-serpentine-talc-minor carbonate and tirodite

(3) G-17, talc-minor clear tremolite

(4) G-19, 21, lavender tremolite (hexagonite)-minor quartz, carbonate, tirodite, and tourmaline

(5) G-24, tremolite-quartz-minor tirodite

Small amounts of carbonate appear as a cementing agent in samples G-16 and G-21. On the basis of a rapid reaction to dilute HCl the cementing carbonate is probably calcite.

TALC

Chemical composition.—The coarsely crystalline talcs (G-1, G-17) taken from the Arnold pit in 1961 and 1966 are nearly pure, only a few small crystals of tremolite appear on careful optical examination of the picked material. Three spectrographic analyses (Table 1) show less than 0.2 percent calcium thus the amount of included tremolite is negligible. Wet chemical analysis (Table 2) confirms the presence of fluorine in the talc structure. Total loss (H_2O+F) on ignition for samples G-1 and G-17 are given in Table 3.

The chemical formula of this talc as given by the analysis G-1 is:

$$Mg_{3.04}Si_{3.96}O_{100}F_{.10}(OH)_{1.90}$$

The analysis shows a few tenths of a percent excess H_2O and this is considered due to analytical error. The small amounts of Fe, Mn, Al, Ca, *etc.*, shown to be present are assumed to be mainly due to the small amount of tremolite.

Partial chemical analysis for H_2O and fluorine were also made of talc (G-17) and tremolite (G-21) sampled from the Arnold pit in 1966 (Tables 1 and 3). Fluorine analyses[1] for a number of other talc specimens obtained

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[1] The samples were fused in 3.5 grs. of sodium carbonate, cooled and leached out in weak sulfuric acid. Samples were then transferred to stills and 100–125 ml. of 1:2 H_2SO_4

TRICLINIC TALC FROM GOUVERNEUR   755

TABLE 1. SPECTROGRAPHIC ANALYSES OF TALC AND TREMOLITE
FROM THE GOUVERNEUR TALC DISTRICT, NEW YORK

	Talc (G-1)[a]	Talc (G-1)[b]	Talc (G-17)[c]	Tremolite (G-21)[d]	Tremolite (G-24)[f]
Si	>10%	20–40	20–40	20–40	20–40
Mg	>10	20–40	20–40	15–30	10–20
Fe	0.03	0.1	0.1	0.2	0.1
Mn	0.03	0.01	<0.005	0.3	1–2
Al	0.03	0.1	0.05	0.2	0.3–1.0
Ti	0.001	0.01	0.005	0.02	0.03
Ni	—[e]	<0.005	<0.005	<0.005	—
Cu	—	<0.005	<0.005	<0.005	—
Li	0.001	0.005	0.005	0.02	—
Na	0.01	0.05	0.05	0.5	0.1–0.3
K	0.001	0.01	0.02	0.1	0.1–0.3
Ca	0.03	0.2	0.1	5–15	5–15
Sr	—	<0.005	—	—	—
Ba	—	<0.005	—	—	—
F	1.0	—	—	0.30[g]	0.31[g]

[a] Arnold pit, Analyst: C. L. Waring, U. S. Geological Survey.

[b] Arnold pit, Analyst: Bernard Snyder, Battelle Memorial Institute.

[e] Arnold pit, Analyst: Bernard Snyder.

[d] Arnold pit, lavender tremolite, Analyst: Bernard Snyder.

[e] — not looked for.

[f] Colorless tremolite, 3/4 mile SW of Wight mine, Balmat, N. Y., Analyst: Bernard Snyder.

[g] By wet chemical analysis.

from worldwide localities were made to obtain more knowledge on the range of fluorine content in this mineral. These fluorine analyses are given in Table 4.

Physical properties.—Talc specimens collected from the Arnold pit show two distinct habits; one variety is fine grained somewhat fibrous in nature (G-16) and is associated with white tremolite. The second variety is coarsely crystalline (G-1, 17), often occurring in nearly mono-mineralic zones. Only the coarse variety was studied by X-ray techniques.

The coarsely crystalline talc forms platy crystals up to 1 cm in width. The crystals are pure white, translucent, with a slight adamantine luster. Some crystals grow as nearly perfect pseudotrigonal pyramids lying on (001). Often the pyramids are truncated by a small (001) face.

added (volume kept below 150 ml.). Fluoride was separated from interfering substances according to the method of Willard and Winter (steam distillation at 165°C). The distillate was collected in 500 ml. volumetric flasks. Fluoride content of the distillate was then determined by a thorium nitrate colorimetric titration.

756 *MALCOLM ROSS, WILLIAM L. SMITH AND WILLIAM H. ASHTON*

TABLE 2. CHEMICAL ANALYSES OF TALC (G-1) FROM ARNOLD PIT, FOWLER, N. Y.

	G-1[a]	Ratios[b]	Ideal[c]
SiO_2	62.68	3.958	63.37
MgO	32.33	3.042	31.88
F	0.48	0.096	—
H_2O (−)	0.33	—	—
H_2O (+)	4.79	1.009	4.75
			100.00
Total	100.61		
$O = F/2$	−0.20		
	100.41		

[a] Arnold pit, collected in 1961, Analysts: Joan Lathouse and R. D. Foltz, Battelle Memorial Institute.

[b] Ratios calculated on basis of $Mg+Si = 7.000$.

[c] $Mg_3Si_4O_{10}(OH)_2$.

Ten talc crystals from sample G-1 were examined with the Buerger precession camera. All crystals gave identical unit-cell parameters; the best measurements are given in Table 5. This talc is triclinic; the space group is $C\bar{1}$ or $C1$, and the structure type is one-layer triclinic (1Tc). In contrast to photographs of the common micas, the $0kl$ and $hk0$ precession precession photographs show a strong triclinic intensity distribution. There is little apparent monoclinic pseudosymmetry in any of the X-ray photographs. X-ray powder data for this material are given in Table 6.

Two talc crystals from sample G-17, one crystal from a sample from the "Talc" mine, Gouverneur, N. Y. (CS-1) and one crystal from a Balsam, North Carolina, sample (CS-2) were also studied by precession

TABLE 3. FLUORINE AND H_2O ANALYSES FOR TALC AND TREMOLITE[a]

Total loss (H_2O+F) in weight percent	Talc (G-1)		Talc (G-17)		Tremolite (G-21)	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
to 110°	0.33	0.0	0.12	0.0	0.05	0.0
110°–550°	0.57 ⎱	4.99	0.19 ⎱	4.96	0.11 ⎱	2.37
550°–1000°	4.70 ⎰		4.33 ⎰		1.45 ⎰	
F	0.48	0.48	0.42	0.42	0.30	0.30
H_2O (+)	4.79	4.51	4.10	4.54	1.26	2.07

[a] Analyst: Joan Lathouse, Battelle Memorial Institute.

TRICLINIC TALC FROM GOUVERNEUR   757

TABLE 4. FLUORINE ANALYSES OF TALC FROM VARIOUS LOCATIONS
AND ORIGINS

Sample	Location and Origin	% F
G-1	Gouverneur talc district, New York	0.48
G-17	Gouverneur talc district, New York	.42
WA-3	Gouverneur talc district, New York, metamorphosed magnesian carbonate sediments.	.45
42771 E	Val Chisone, Italy	.44
23	Val Chisone, Italy metamorphosed magnesian carbonate sediments.	.31
25	Murphy, North Carolina, metasomatic replacement of magnesian carbonate sediments.	.36
30	Inyo County, California, replacement of quartzite along dolomite contact.	.34
26	Brumado, Bahia, Brazil, magnesia metasomatism of siliceous carbonate sediments.	.29
11	Casa Nova, Bahia, Brazil, lenses of replaced siliceous magnesian carbonate sediments.	.27
S 423	Windsor County, Vermont, schistose talc-carbonate rock, not of ultrabasic origin, but associated with ultrabasic body.	.26
7	Allamoore, Texas, metamorphism of interbedded limestone and magnesia rich tuff.	.20
8	Madoc, Ontario, Canada, metamorphosed magnesian carbonate sediments.	.18
31	Dillon, Montana, replacement of dolomite in fracture zones.	.18
29	Flinders Range, South Australia, metasomatism of silicified magnesian carbonate sediments.	.17
32	Esmeralda County, Nevada, metamorphosed quartzite lens in dolomite.	.17
28	Tong yang, South Korea, metamorphosed magnesian carbonate sediments.	.16
14	Dausa, Rajasthan, India, metamorphosed magnesian carbonate sediments.	.11
33	Tamaulipas, Mexico, hydrothermally altered basic dike, enclosed in serpentinized schist.	.04
WA-1b	Lamoille County, Vermont, automorphic alteration of ultrabasic rock, associated with serpentine.	.04
3	Zambales, Philippines, altered ultrabasic rock, associated with serpentine.	.01
27	Transvaal, South Africa, altered ultrabasic rock, associated with serpentine.	.007
13	Providence County, Rhode Island, associated with serpentine pods in greenstone.	.004

Note: Sediments refers to metamorphic rocks of sedimentary origin.

758   *MALCOLM ROSS, WILLIAM L. SMITH AND WILLIAM H. ASHTON*

TABLE 5. UNIT-CELL DATA FOR TALC

	Arnold pit, G-1		A	B	C	D	E
	C^a	P^b	P^b				
a (A)	5.27_9	5.27_5	5.29	5.26	5.27	5.27	5.28_7
b (A)	9.13_7	5.27_5	5.30	9.10	9.13	9.13	9.15_8
c (A)	9.44_8	9.45_0	9.47	18.81	18.88	18.94	18.95
α	90°46′	84°53′	86°6′				
β	98°55′	98°59′	98°54′	100°0′	100°15′	100°40′	99°30′
γ	90°0′	120°0′	120°0′				
System	triclinic	triclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Diffraction symbol	$\bar{1}C_*$	$\bar{1}P_*$	$\bar{1}P_*$	C_*/c	C_*/c	—	—
Structure type	1Tc	1Tc	1Tc	$2M_1$	$2M_1$	$2M_1$	$2M_1$

[a] *C*-setting (preferred setting).

[b] *P*-setting (conventional setting).

A   Rayner and Brown (1966), Harford County, Md.
B   Gruner (1934), Harford County, Md.
C   Hendricks (1938), Harford County, Md.
D   Zvyagin and Pinsker (1949).
E   Stemple and Brindley (1960), Manchuria.

techniques. All give the same unit-cell data as that given in Table 5.

Ross, Takeda, and Wones (1966) have shown that many mica samples are composed of more than one polytype. Thus a number of crystals from a given layer silicate sample should be examined before assuming the specimen is homogeneous. Talc G-1 from the Arnold pit appears to be so. Our present study coupled with that of Rayner and Brown (1966) suggests that most talc is triclinic. Previous reports of the monoclinic form may be in error.

Unit-cell data for talcs studied previously are compared to that of the Arnold pit talc in Table 5. X-ray data for sample G-1 is given both in the *C*-centered setting and in a conventional primitive cell setting so that it may be compared to the results of Rayner and Brown. The transformation matrix from the *C*-centered unit-cell to the conventional primitive cell is: $100|-1/2-1/2\,0|001$. The *C*-centered setting is preferred for it facilitates comparison with other layer silicate structures. Rayner and Brown examined the same specimen as that studied by Hendricks in 1938 and probably is also identical to that examined by Gruner in 1934. Thus, the only evidence for a two-layer monoclinic talc is the work of Stemple and Brindley (1960) and Zvyagin and Pinsker (1949).

The optical properties of the Arnold pit talc (G-1) are: biaxial positive, optic angle variable ranging from 0° to 10°, $\alpha=1.545\pm0.002$, $\beta=\gamma=1.584\pm0.002$. The value of the optic angle is highly dependent on the

TRICLINIC TALC FROM GOUVERNEUR   759

TABLE 6. OBSERVED[a] AND CALCULATED[b] X-RAY POWDER DATA FOR TALC (G-1)
FROM THE ARNOLD PIT, GOUVERNEUR, N. Y., MINING DISTRICT

C-setting hkl	P-setting hkl	d (calc.) Å	d (obs.) Å	I[c]
001	001	9.333	9.34	vs
002	002	4.667	4.68	w
020	010	4.568	4.56	s
$\bar{1}$10	100	4.531		
110	$\bar{1}$10	4.523		
$\bar{1}\bar{1}$1	$\bar{1}$11	4.316		
$\bar{1}$11	$\bar{1}$01	4.298		
0$\bar{2}$1	011	4.125	4.14	vw
021	0$\bar{1}$1	4.082		
1$\bar{1}$1	101	3.885	3.85	vw
111	1$\bar{1}$1	3.862		
$\bar{1}\bar{1}$2	$\bar{1}$12	3.504	3.43	w
$\bar{1}$12	$\bar{1}$02	3.481		
0$\bar{2}$2	012	3.287		
022	0$\bar{1}$2	3.243		
003	003	3.111	3.115	s
1$\bar{1}$2	102	3.061		
112	1$\bar{1}$2	3.040		
$\bar{1}\bar{1}$3	$\bar{1}$13	2.751		
$\bar{1}$13	$\bar{1}$03	2.733		
$\bar{1}$30	110	2.632		
130	$\bar{1}$20	2.627	2.632	wm
$\bar{2}$01	$\bar{2}$11	2.617		
200	$\bar{2}$10	2.606	2.598	m
$\bar{1}$31	$\bar{1}$21	2.590		
0$\bar{2}$3	013	2.588		
$\bar{1}$31	$\bar{1}\bar{1}$1	2.578		
023	0$\bar{1}$3	2.555		
1$\bar{3}$1	111	2.490	2.48	s-d
131	1$\bar{2}$1	2.472		
$\bar{2}$02	$\bar{2}$12	2.442		
1$\bar{1}$3	103	2.424		
201	2$\bar{1}$1	2.415		
113	1$\bar{1}$3	2.409		
$\bar{1}$32	$\bar{1}$22	2.382		
$\bar{1}$32	$\bar{1}\bar{1}$2	2.361		
004	004	2.333	2.336	vw

[a] CuKα radiation, Ni filter ($\lambda = 1.5418$ Å). Camera diameter: 114.59 mm. Lower limit 2θ measurable: approximately 8° (11.0 Å).

[b] Calculated from the following unit-cell parameters: $a = 5.275$, $b = 9.137$, $c = 9.448$ Å, $\alpha = 90°46'$, $\beta = 98°55'$, $\gamma = 90°0'$, space group $C\bar{1}$. All calculated spacings are given to $d = 2.284$ Å.

[c] vs (very strong), s (strong), ms (medium strong), m(medium), wm (weak medium), w (weak), vw (very weak), d (diffuse).

TABLE 6. (Continued)

C-setting hkl	P-setting hkl	d (calc.) Å	d (obs.) Å	I°
040	020	2.284	2.284	vw
			2.219	m-d
			2.103	m-d
			1.994	wm
			1.871	m
			1.731	w
			1.688	vw-d
			1.558	w
			1.527	ms
			1.515	w
			1.320	w
			1.296	w
			1.271	vw

amount of twinning in the crystal; highly twinned crystals have low optic angles.

AMPHIBOLES

Chemical properties.—Two varieties of tremolite occur in the Arnold pit specimens; one lavender to pink in color (G-19, 21), the other pure white (G-16, 17). The lavender form occurs in large prismatic crystals several millimeters long. The varietal name "hexagonite" is often used to describe this tremolite; the type material reported as coming from Edwards, St. Lawrence County, N. Y. (Dana, 1892, p. 389, 393). The white variety of tremolite is associated with the "limy talc" (G-16) and to a small extent, with the coarsely crystalline talcs (G-1, 17). The lavender tremolite occurs in nearly mono-mineralic zones between the massive talc ore and hanging wall dolomite.

An exceptionally well-crystallized colorless tremolite rock collected 3/4 of a mile southwest of the Wight mine was also examined (G-24). Spectrographic analyses of the lavender and colorless varieties (G-21, G-24) are given in Table 1. Quantitative analyses for H_2O and fluorine for the G-21 tremolite are given in Table 3. The analyzed samples G-21 and G-24 contain a small amount of tirodite and quartz.

Engel (1962, p. 309) gives complete mineral analyses for two tremolites collected from the old Arnold mine. These analyses are recalculated in our Table 7. The various analyses (Table 1, 7) show that the Gouverneur tremolites have a nearly end-member composition with some Mn^{2+}, K, and Na replacing calcium, F replacing (OH), and Al replacing Si.

There are four different occupied cation sites in the tremolite crystal

TABLE 7. TREMOLITE CHEMICAL ANALYSES FROM ENGEL (1962, p. 309)

| | Weight percent | | | Atomic ratios[e] | | | |
	9a	15b		9b		15	
SiO_2	57.83	57.76	Si	7.915		7.897	8.001
Al_2O_3	0.57	0.64	Al	0.092	8.028	0.104	
Fe_2O_3	0.20	0.00	Fe^{3+}	0.021			
MgO	24.25	24.73	Mg	4.945		5.038	
FeO	0.11	0.14	Fe^{2+}	0.012	5.285	0.016	5.066
TiO_2	0.03	0.05	Ti	0.003		0.005	
MnO	2.81	0.06	Mn^{2+}	0.325		0.007	
CaO	11.42	13.27	Ca	1.675		1.944	
K_2O	0.14	0.09	K	0.025	1.744	0.016	2.033
Na_2O	0.17	0.28	Na	0.044		0.073	
H_2O^-	0.06	0.13					
H_2O^+	2.09	2.38	OH	1.907	(1.820)	2.170	(1.882)
F	0.41	0.26	F	0.178	0.180	0.113	0.118
Cl	0.01	0.02	Cl	0.002		0.005	
CO_2	0.00	—					
	100.10	99.81					
$O=F+Cl$	0.17	0.11					
	99.93	99.70					

[a] Arnold No. 3 mine, 11th level, Fowler, N. Y.

[b] Arnold mine, 14th level, Fowler, N. Y.

[e] Number of ions on the basis of: number of oxygen atoms = 22.00 and (OH) = 2.00-F-Cl.

structure, designated M_1, M_2, M_3, and M_4. The smaller metal atoms such as Mg and Fe enter the M_1, M_2, and M_3 sites whereas the larger cations such as Ca and Na enter the large M_4 site. With our present knowledge of amphibole structure we do not expect any alkalies or alkaline earths to enter the M_1, M_2, or M_3 sites. Ideally the M_4 site should take up 2.00 calcium atoms per formula unit. The small cations, however may enter the M_4 sites in appreciable quantities replacing some of the calcium or sodium.

Physical properties.—X-ray studies of the lavender and white tremolite were made using both single crystal and X-ray powder techniques. The lavender tremolite specimens (G-19, 21) are essentially mono-mineralic. The crystals appear optically perfect with no evidence of twinning, exsolution or alteration. Single crystal photographs show tremolite G-21 to be monoclinic, space group $C2/m$, Cm, or $C2$ with $a = 9.81_6$ Å, $b = 18.04$,

762   *MALCOLM ROSS, WILLIAM L. SMITH AND WILLIAM H. ASHTON*

TABLE 8. UNIT-CELL DATA FOR TREMOLITES FROM THE
GOUVERNEUR, NEW YORK TALC DISTRICT

	G-21[a]		G-24[e]		G-16[d]
	Single crystal	Powder[b]	Single crystal	Powder[b]	Single crystal
a (Å)	9.81_6	9.818 (5)	9.79_6	9.812 (2)	9.81_8
b (Å)	18.04	18.047 (8)	18.04	18.077 (3)	18.04
c (Å)	5.27_6	5.275 (3)	5.28_1	5.273 (2)	5.281
β	104°30′	104°39′ (3′)	104°25′	104°43′ (2′)	104°35′
V (Å³)	904.4	904.2 (6)	903.9	904.5 (3)	904.2
System	monoclinic		monoclinic		monoclinic
Diffraction symbol	$C*/*$		$C*/*$		$C*/*$

[a] Lavender tremolite, Arnold pit, St. Lawrence County, N. Y.

[b] Obtained from least-squares refinement of powder data given in Table 9. Errors in thousandths of an Ångstrom and minutes given in parentheses.

[e] White tremolite, 3/4 mile SW Wight mine, N. Y.

[d] White tremolite, Arnold pit, St. Lawrence County, N. Y.

$c = 5.27_6$, and $\beta = 104°30′$. The $h0l$ precession photographs exposed to unfiltered molybdenum radiation for 100 hours show extremely weak spots representing a second phase. X-ray data for this tremolite are summarized in Table 8. X-ray powder data for tremolite G-24 and G-21 are given in Table 9. Spectrographic analysis was given in Table 1.

In addition to lavender tremolite described above two white tremolites (G-16, G-24) were examined by X-ray single crystal techniques. Both tremolites show, under crossed nicols, thin lamellae oriented parallel to the (10$\bar{1}$) plane. In sample G-24 the lamellae are so distinct they can be seen in the hand specimen with a low power binocular microscope.

Precession photographs of both specimens give unit-cell data close to that of the lavender tremolite (Table 8). Superimposed on the strong single-crystal patterns of the host tremolite phase is a weaker pattern of a second amphibole. This second phase is a clino-amphibole having space group symmetry $P2_1/m$ or $P2_1$ with $a = 9.48$ Å, $b = 18.03$, $c = 5.29$, and $\beta = 101°55′$.

The unit-cell data for the $P2_1/m$ amphiboles (G-16 and G-24) are given in Table 10 where the data is compared to that obtained by Bown (1966) on a similar specimen. As pointed out by Bown, who first reported existence of this $P2_1/m$ amphibole, the two coexisting amphibole phases have a common b-axis with the b-dimensions almost identical. The

TABLE 9. OBSERVED[a] AND CALCULATED[b] X-RAY POWDER DATA FOR WHITE
(G-24) AND LAVENDER (G-21) TREMOLITE FROM THE
GOUVERNEUR, N. Y. MINING DISTRICT

hkl	Tremolite, G-24			Tremolite, G-21		
	d (calc.) Å[e]	d (obs) Å	I	d (calc.) Å[d]	d (obs) Å	I
020	9.039	9.054	15	9.024		
110	8.403	8.410	40	8.405		
001	5.100	5.092	20	5.103		
130	5.087			5.082	5.046	60
$\bar{1}$11	4.873	4.875	10	4.873	4.866	5
200	4.745	4.751	10	4.749	4.739	10
040	4.519	4.523	30	4.512	4.514	10
021	4.441			4.442		
220	4.201	4.209	15	4.203	4.197	50
$\bar{2}$01	4.020	4.028	5B	4.021		
111	3.980			3.984		
13$\bar{1}$	3.875	3.880	15	3.873	3.878	10
$\bar{2}$21	3.673			3.673		
041	3.382			3.380 ⎫		
131	3.379			3.380 ⎬	3.373	25
150	3.379			3.374 ⎭		
240	3.273	3.272	65	3.271	3.274	85
310	3.116	3.120	100+	3.119	3.115	100+
201	3.103			3.107		
$\bar{3}$11	3.016			3.016	3.013	5
060	3.013			3.008		
$\bar{2}$41	3.004	3.004	5	3.002		
$\bar{1}$51	2.942	2.944	45	2.939 ⎫		
					2.942	35
221	2.935			2.937 ⎭		
330	2.801	2.802	25	2.802		
$\bar{3}$31	2.727			2.727	2.727	20
151	2.706	2.712	100+	2.705	2.709	60
$\bar{1}$12	2.608			2.609		
061	2.594	2.594	35	2.591	2.589	15
241	2.558	2.557	5	2.559		

[a] CuKα radiation, Ni filter ($\lambda = 1.5418$ Å). Pattern taken with North American Philips X-ray diffractometer internally standardized with sodium fluoride. Specimens contain a small amount of quartz and tirodite.

[b] All calculated interplanar spacings are given down to $d = 2.530$ Å. Calculated spacings less than this are given only where indexable to an observed spacing.

[e] Calculated from the following unit-cell parameters: $a = 9.812$ Å, $b = 18.077$, $c = 5.273$, $\beta = 104°43'$, space group $C2/m$. Composition by electron microprobe analysis: $Ca_{1.5}Mn_{0.3}Mg_{5.2}Si_8O_{22}(OH, F)_2$.

[d] Calculated from the following unit-cell parameters: $a = 9.818$ Å, $b = 18.047$, $c = 5.275$, $\beta = 104°39'$, space group $C2/m$.

764   *MALCOLM ROSS, WILLIAM L. SMITH AND WILLIAM H. ASHTON*

TABLE 9. (*Continued*)

hkl	Tremolite, G-24			Tremolite, G-21		
	d (calc.) Å^c	d (obs) Å	I	d (calc.) Å^d	d (obs) Å	I
002	2.550			2.552		
260	2.543			2.541		
$\bar{2}$02	2.530	2.530	25	2.530	2.531	20
350	2.381	2.379	15	2.380	2.379	100+
$\bar{3}$51	2.335			2.334	2.336	45
420	2.295	2.295	20	2.296	2.295	20
$\bar{3}$12	2.272	2.267	20	2.272	2.268	20
242	2.208			2.207	2.210	5
171	2.182	2.182	5	2.180	2.177	10
132	2.164			2.166		
		2.164	55			
261	2.162			2.161	2.161	25
$\bar{1}$52	2.130	2.132	5	2.129		
202	2.040			2.043	2.043	5
		2.046	10			
280	2.040			2.038		
351	2.015	2.015	25	2.015	2.015	30
370	2.000	1.999	10	1.999	1.998	100+
190	1.965			1.962		
					1.961	15
$\bar{4}$22	1.962	1.961	10	1.962		
510	1.888	1.887	30	1.889	1.892	35
460	1.864	1.864	15	1.864	1.864	10
$\bar{4}$42	1.837			1.836	1.836	10
530	1.810			1.812	1.810	15
441	1.805	1.805	10	1.806		
172	1.726			1.725		
					1.720	15
$\bar{2}$23	1.716			1.716		
$\bar{3}$72	1.713	1.710	5	1.712		
$\bar{2}$82	1.685	1.685	15	1.684		
					1.685	10
$\bar{1}$33	1.683			1.683		
		1.675	10			
$\bar{2}$, 10, 1	1.649			1.646		
		1.649	40		1.648	30
461	1.648			1.648		
1, 11, 0	1.619	1.617	15	1.617	1.618	30
$\bar{4}$03	1.586			1.586		
					1.585	20
600	1.582			1.583		
					1.561	5

TABLE 9. (*Continued*)

hkl	Tremolite, G-24			Tremolite, G-21		
	d (calc.) Å[c]	d (obs) Å	I	d (calc.) Å[d]	d (obs) Å	I
$\bar{5}$71	1.555	1.555	10	1.555 }	1.554	20
402	1.551			1.553 }		
					1.530	10
1, 11, 1	1.524	1.525	10	1.522		
282	1.514			1.514	1.514	100+
$\bar{2}$63	1.512	1.511	10	1.511		
$\bar{4}$82	1.502	1.503	20	1.501		
$\bar{2}$, 10, 2	1.471	1.470	10	1.469	1.468	5
0, 12, 1	1.445	1.445	10	1.443		
		1.433	35		1.435	75
$\bar{5}$91	1.398	1.398	10			
$\bar{7}$31	1.365	1.365	15			

a-axes of the tremolite and $P2_1/m$ amphibole lie in a common (010) plane and at an angle of 2°30′ of one another. The study by Bown was made on a tremolite from the Wight mine, St. Lawrence County, N. Y. showing "extremely fine (001) lamellae." His material is probably very similar in composition to specimens G-16 and G-24. In the $I2/m$ setting of Bown

TABLE 10. UNIT-CELL DATA FOR THE SECOND AMPHIBOLE PHASE
EXSOLVED FROM THE GOUVERNEUR TREMOLITES

	G-24[a]	G-16[b]	Bown (1966)[e]	Mg-cummingtonite[d]
a (Å)	9.50$_2$	9.47$_6$	9.51	9.467
b (Å)	18.04	18.03	17.95	17.937
c (Å)	5.28$_4$	5.28$_5$	5.27	5.292
β	102°25′	101°55′	102°0′	102°14′
V (Å^3)	884.6	883.5	880.0	878.1
System	monoclinic	monoclinic	monoclinic	monoclinic
Diffraction symbol	$P2_1/*$	$P2_1/*$	$P2_1/*$	$C*/*$?

[a] Data obtained from the same single crystal patterns as those of tremolite G-24 (Table 8).

[b] Data obtained from the same single crystal patterns as those of tremolite G-16 (Table 8).

[e] Cell edges transformed from the I-centered cell: $a=9.87$ Å, $b=17.95$, $c=5.27$, $\beta=109.5°$, space group $I2/m$.

[d] Unit-cell data of an iron free cummingtonite, $Mg_7Si_8O_{22}(OH)_2$, as extrapolated by Viswanathan and Ghose (1965).

the lamellae are oriented parallel to the (001) plane. Bown suggested that the lamellae are clino-anthophyllite.

Ross, Papike and Weiblen (1968) have made a more complete study of the composition and structural state of the amphiboles in sample G-24 and also have studied a sample of the manganoan amphibole tirodite (Segeler, 1961) from the International Talc mine No. 3 in the nearby Talcville, N. Y. area. X-ray precession photos and least-squares powder refinement of tirodite give the following unit-cell data: $a = 9.550 \pm 0.001$ Å, $b = 18.007 \pm 0.003$, $c = 5.298 \pm 0.001$, $\beta = 102°39' \pm 1'$, space group $P2_1/m$ or $P2_1$. The single crystal photos also show a weaker pattern of a second amphibole oriented parallel to the $(10\bar{1})$ plane of tirodite. The unit-cell data for this second phase is: $a = 9.78$ Å, $b = 17.99$, $c = 5.27$, $\beta = 104°25'$, space group $C2/m$. The $(10\bar{1})$ lamellae can be seen optically in the tirodite grains. Electron microprobe scans over the Talcville tirodite give the approximate composition as $Ca_{0.4}Mn_{1.2}Mg_{5.4}Si_8O_{22}(OH,F)_2$. The lamellae are about one micron thick and have a much higher calcium and lower manganese content than the host tirodite phase.

Microprobe examination of sample G-24 shows that in addition to the crystals of calcium-rich tremolite there are a few grains of a manganese-rich amphibole. The lamellae in the tremolite are manganese-rich and similar in composition to tirodite. The lamellae in the Mn-rich amphibole are calcium-rich. The approximate compositions of the tremolite and Mn-rich host phases are $Ca_{1.5}Mn_{0.3}Mg_{5.2}Si_8O_{22}(OH, F)_2$ and $Ca_{0.2}Mn_{0.9}Mg_{5.9}Si_8O_{22}(OH, F)_2$ respectively. Chemical and X-ray evidence leaves no doubt that sample G-24 contains two amphiboles, tremolite and tirodite, with tremolite exsolving tirodite and tirodite exsolving tremolite. It is estimated that tirodite composes about 5 weight percent of the sample. The tirodite sample from Talcville is an analogue to sample G-24, the major phase is tirodite, the minor exsolved phase is tremolite.

In order to obtain more precise unit-cell data for the lavender and white tremolites (G-21 and G-24) the X-ray powder diffractometer data (Table 9) was subjected to least-squares refinement. The refined parameters are compared to the single crystal X-ray data in Table 8. The amount of tirodite in sample G-21 is probably less than one weight percent and in sample G-24, probably less than 5 weight percent. No lines of tirodite could be detected in either sample and thus should not have effected the refinement.

The optical properties of all three tremolites studied (G-16, G-21 and G-24) are nearly identical (biaxial negative, $\alpha = 1.604 \pm 0.002$, $\beta = 1.612 \pm 0.002$ and $\gamma = 1.628 \pm 0.002$), suggesting similar chemical compositions. The lavender variety does not show $(10\bar{1})$ lamellae although the X-ray

photographs show definitely that the second amphibole phase is present but composing probably less than one volume percent of the crystal. The lamellae are much more pronounced in G-16 and G-24 and the X-ray diffraction single crystal patterns of the lamellae are relatively strong with many reflections appearing in the $h0l$, $h1l$, and $h2l$ nets.

Discussion

Talc.—Talc deposits may form by the metamorphism of carbonate rocks, by the replacement of silicified carbonate rocks, or by the alteration of ultramafic rocks. There are reported occurrences of talc formed from mafic and felsic igneous rocks, pegmatites, tuff, and low magnesian sediments; however, these involve complex and unique conditions that are atypical of the major occurrences. Talc bodies may also form by contact metamorphism in rare instances where the chemical conditions are correct.

Twenty-two specimens of essentially pure talc obtained from nineteen different deposits have been analyzed for fluorine content (Table 4). All of the talc samples were found to contain fluorine. Although too few samples have been studied to permit firm conclusions to be drawn, the following relationships may be inferred:

(a) Talc from deposits believed to be derived from the metamorphism of carbonate sedimentary rocks, formed by the replacement of silicified carbonate rocks, or occurring in talc-carbonate-amphibole schists, were found to contain 0.11 to 0.48 percent fluorine.

(b) Talc from the five deposits believed to be derived from the alteration of mafic or ultramafic rock, and which are intimately associated with serpentine, show fluorine content below 0.04 percent.

The present study coupled with that of Rayner and Brown (1966) definitely shows that the common variety of talc has a one-layer triclinic structure. Other polytypes, if they occur will probably be rare compared to the 1Tc form. To summarize, talcs from the following localities have been shown to have the one-layer triclinic structure:

(1) Harford County, Maryland, U.S.N.M. 82519
(2) Arnold pit, St. Lawrence County, New York
(3) "Talc" mine, St. Lawrence County, New York
(4) Balsam, North Carolina.

Tremolite.—Engel and Engel (1968) suggest that the temperature of metamorphism in the Gouverneur mining district in the is 500° to 600°C range. Some of the tremolites were enriched in manganese at the expense of calcium and sodium (*e.g.*, Table 7, analysis 9b). The evidence given by Ross, Papike and Weiblen (1968) shows that the manganese-enriched

768   *MALCOLM ROSS, WILLIAM L. SMITH AND WILLIAM H. ASHTON*

tremolite coexisted with a second amphibole tirodite which was enriched in calcium. On cooling both phases unmixed to produce the $(10\bar{1})$ lamellae. Apparently at high temperatures the M_4 site can hold appreciable quantities of manganese. The appearance of exsolution lamellae in tremolite should be very useful in understanding the paragenesis of the Gouverneur schists and can also give information on the extent of solid-solution in tremolites.

Alteration of the tremolite-bearing schists.—Optical and X-ray examination of a number of tremolite rocks from the Gouverneur area show the following retrograde alteration sequences:

(1) Sample CS-1, "Talc" mine
　　　　　tremolite+talc→anthophyllite+talc
(2) Sample G-2, International talc mine, N. Y.; G-5, Fullerville, N. Y.
　　　　　tremolite→anthophyllite→talc
(3) Sample G-6, Fowler, N. Y.
　　　　　anthophyllite→talc
(4) Sample G-18, Aronold pit
　　　　　tremolite→serpentine
(5) Sample G-26, Wight mine
　　　　　tremolite→anthophyllite→talc?

Tremolites CS-1, G-5, and G-26 show prominent exsolution lamellae. Stemple and Brindley (1960) give evidence for the transformation tremolite→talc in a specimen from the Gouverneur area.

All of the very fine grained talc, anthophyllite, and serpentine noted in the Gouverneur schists appear to have grown by a latter alteration of tremolite or anthophyllite. The coarsely crystalline talc (*e.g.*, G-1, G-17) is associated with clear unaltered tremolite and appears to be a primary metamorphic assemblage; not a result of any retrograde alteration. The coarsely crystalline talc is not valuable commercially because of its poor milling quality. The fine-grained alteration products of the amphiboles (*e.g.*, G-16, G-18) forms the commercial ore. The superior milling quality of this ore is probably due to the fine-grained nature of the magnesium silicate alteration products.

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Exhibit 31

A Structural Study of Talc and Talc-Tremolite Relations

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About forty specimens of talc have been examined by X-ray powder methods. Variations in the degree of crystallinity of the mineral have been observed, but no evidence has been obtained for polymorphic structural varieties. Single-crystal data have confirmed the two-layer monoclinic cell. Little evidence has been obtained of talcs containing mixed-layer sequences. Electron micrographs have revealed a variety of platy and fibrous forms, and in the latter a close structural relation between talc and tremolite has been established. Talcs prepared synthetically in the presence of aluminum showed small lattice parameter differences from talcs prepared in the absence of aluminum, and the results are consistent with the substitution of small percentages of Al ions in the talc structure. New X-ray powder data and unit-cell parameters for talc and tremolite are listed.

Table I.   Unit-Cell Parameters of Talc (a.u.)*

	Gruner†	Hendricks‡	Present writers§
a	5.27	5.28 ± 0.02	5.28_7
b	9.12	9.12 ± 0.03	9.15_8
c	18.85	18.92 ± 0.05	18.95
β	100° ± 5′	100° 15′ ± 15′	99° 30′

* Gruner and Hendricks values converted from kX units to angstrom units by the factor 1.002.

† FeK radiation, unfiltered; 114.6-mm.-diameter camera; talc from Harford County, Maryland.

‡ CuK radiation; rotation and Weissenberg data; talc from Harford County, Maryland.

§ CuKα radiation, filtered; 114.6-mm.-diameter camera and Philips high-angle X-ray diffractometer; talc from Manchuria (purified to remove magnesite).

I. Introduction

THE hydrated magnesian silicate, talc, has received less detailed structural study than most other common layer silicate minerals. The reasons for this apparent neglect are difficult to discover since talc is known to occur in various morphologic varieties, principally foliated, laminated, massive, and fibrous.

Chemically, talc approximates the ideal chemical composition $3MgO \cdot 4SiO_2 \cdot H_2O$ or $Mg_3Si_4O_{10}(OH)_2$, for which the weight proportions are MgO 31.9%, SiO_2 63.4%, H_2O 4.75%. The purer talcs come near this ideal composition, but less pure talcs contain additional oxides, notably Al_2O_3 and CaO, and whether these form part of the mineral structure or are contained in impurities is not always clear and may be difficult to ascertain. Among common impurities are chlorites and tremolite, the former introducing Al_2O_3 and the latter CaO into the oxide composition.

The present study was undertaken to determine if talc exists in more than one structural form. X-ray and electron diffraction methods have been used, the latter in conjunction with electron microscope studies. An unexpected structural relation between talc and tremolite has been discovered in the fibrous forms of talc. Optical studies of the talc-tremolite association have been made by H. D. Wright and are reported separately by him.*

II. X-Ray Data for Talcs

(1) Powder Studies

The X-ray powder diagram of talc was studied by Gruner[1] (1934), who concluded that the structure was monoclinic, having two structural layers per unit cell and the cell parameters as given in Table I.

Pask and Warner[2] (1954) reported X-ray diffractometer patterns of talc for which they found "an excellent match" with data given in the X-ray Powder Data File. Some changes in relative intensities were observed and diffuse scattering was found. They also made differential thermal analyses and considered that changes of shape and position of the endothermic peak might be the result of mixed-layer sequences in the crystal structure, but little evidence was given to substantiate this hypothesis.

In the present work, evidence has been sought for polymorphic variations in talc and for data which might confirm the Pask-Warner supposition of mixed-layer sequences. Since polymorphic variations in other layer minerals (e.g., the micas and the kaolin minerals) can be established on the basis of powder data, a powder diffraction survey was undertaken of about forty talcs.

Variations in the diffractometer patterns taken with CuKα radiation were observed and Fig. 1 shows some typical results. The variations may be attributed to (1) variations in the degree of preferential orientation of the platy particles, (2) variation in the amount of lattice disorder, and (3) presence of other substances.

Curve (a) in Fig. 1 is for a purified and well-crystallized Manchurian talc; there is some preferential orientation of the particles which is shown by the enhancement of the basal $00l$ reflections. The mineral exhibits considerable lattice disorder as shown by the spread of the 020 peak toward higher 2θ values. This disorder is of the layer displacement type commonly found in layer lattice silicates. Curve (b) is for a foliated talc from Harford County, Maryland.

* See pp. 42–43, this issue.

[1] J. W. Gruner, "Crystal Structures of Talc and Pyrophyllite," Z. Krist., 88 [5–6] 412–19 (1934); Ceram. Abstr., 14 [2] 50 (1935).

[2] J. A. Pask and M. F. Warner, "Fundamental Studies of Talc: I, Constitution of Talcs," J. Am. Ceram. Soc., 37 [3] 118–28 (1954).
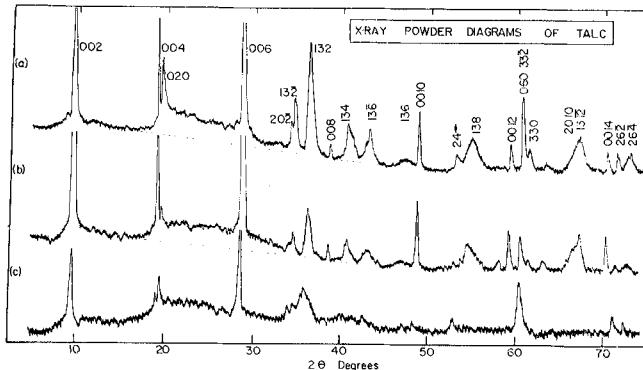
Fig. 1.   X-ray diffractometer traces of talcs of different degrees of crystallinity, CuKα radiation.   (a) Purified sample of talc from Manchuria, (b) foliated talc from Harford County, Maryland, (c) dark green, massive talc from Chester County, Pennsylvania.

The powdered sample exhibits considerable orientation and there is probably more lattice disorder than in the powdered Manchurian talc.   Curve (c) is for a dark green, massive talc from Chester County, Pennsylvania.   This specimen is highly disordered and, apart from the basal reflections, few clear reflections remain.   The 132, 13$\bar{2}$ lines are broadened into a single broad peak, and the 00,10 and 00,12 basal reflections, usually strong, are scarcely seen.   Disorder of this magnitude is rare among the talc specimens which the writers have examined.

When the powder diagram is indexed on the basis of the two-layer monoclinic cell, all observed reflections have l indices which are even; i.e., on the basis of the indexing there is no evidence for a two-layer cell.   Well-exposed photographs were taken with a 114-mm. camera with CuKα radiation, and in a few cases with CrKα radiation and a helium-filled camera, and a few additional very weak reflections were obtained which might have odd l indices; e.g., $d = 3.430$ may be (113), $d = 2.892$ may be (025). The powder data are recorded in the Appendix (see p. 41), where they are compared with Gruner's results, which have been converted from kX to angstrom units by the factor 1.002.

The lattice parameters derived from the present results are recorded in Table I.   They agree well with data obtained by Hendricks[3] (1938) (see later discussion) but are consistently higher than Gruner's values.   This difference is also found in the recorded spacings, the present values being about 0.4% larger than those of Gruner.

Another feature of the indexed diagram is that the k indices, with rare exceptions, are multiples of 3 in accordance with random or nearly random layer displacements of $nb/3$.   The main exception is the 020 reflection which occurs as a diffuse band with strong intensity at the low-angle limit; the fact that d (obs) is somewhat less than d (calc) for the low-angle termination agrees with the "two-dimensional" character of this diffraction.   Brindley and Robinson[4] (1948) discussed in detail similar diffraction effects for halloysite where d (obs) $<$ d (calc) by 0.03 a.u. for the 020 diffraction band.   Another exception is the reflection at $d = 1.725$, marked 24– on curve (a), Fig. 1, which may be a 24$\bar{2}$

reflection or a composite two-dimensional 240, 150, 310 diffraction band.   The very weak reflections 113 and 025 mentioned previously are very doubtful because scattering in the directions of these reflections will be part of the 020, 110 diffraction band.

No clear evidence was obtained for mixed-layer sequences apart from the exceptional case illustrated by curve (c), Fig. 1, where the spreading of the 002 reflection and the virtual absence of the 00,10 and 00,12 reflections suggest the possibility of an irregular layer sequence.   For practically all the talcs examined in the present work, the X-ray data indicate regular layer sequences and provide no support for the hypothesis of Pask and Warner.   Long-exposure powder photographs, however, often revealed traces of impurities, such as mica and chlorite, not visible in the diffractometer traces, which might possibly explain the variations in the thermal data which they observed.

The main conclusion from the powder diffraction survey is that there is no evidence for polymorphic varieties.   However, since the evidence for the two-layer cell is also essentially nonexistent *from powder data*, and since all the powdered samples have considerable disorder of the b-axis displacement type, it is necessary to be cautious in concluding from powder data alone that polymorphic varieties do not exist.   It is very probable that the interlayer binding forces in talc are so very weak that the structure is considerably disordered by any mechanical process.

(2)   Single-Crystal Studies

Relatively few talcs furnish single crystals good enough for single-crystal techniques, but foliated talcs such as the material from Harford County, Maryland, are an exception. These were examined by Hendricks[3] (1938), and his observations have been fully confirmed in the present work.   The data confirm unambiguously the two-layer structure of the unit cell, and it is evident that powder diffraction analysis has serious limitations in work of this kind.   The unit-cell parameters obtained by Hendricks are listed in Table I.

Too few single crystals have been examined in this work to state categorically that polymorphic varieties do not exist.   Rotation and Weissenberg photographs of talc crystals from Bare Hills, Maryland, from Alabama, from Providence, Rhode Island, and from Transvaal showed close agreement and indicated the absence of significant structural differences.

The objectives of the present study precluded any more detailed analysis of the talc structure.   The observational data support the work of Gruner[1] and of Hendricks.[3]

(3)   Indexed Powder Diagram of Tremolite

In studying the close association of tremolite with talc, a more precise powder diagram of tremolite was found to be necessary.   The three patterns available in the X-ray Powder Data File (1958 edition) were found to be collectively unsatisfactory.   An indexed diagram was prepared and the results are listed in the Appendix.   An incidental aspect of this work is that the unit-cell parameters found in this work for tremolite are larger than those given by Warren[5] (1929) and are in better accord with data for other amphiboles[6,7] (see Table II).   Zussman[6] (1955) commented that the order of increasing unit-cell volume, tremolite-crocidolite-actinolite, was "somewhat surprising" because the atomic constitution "would certainly not place tremolite as the

[3] S. B. Hendricks, "Crystal Structure of Talc and Pyrophyllite," *Z. Krist.*, **99**, 264–75 (1938); *Ceram. Abstr.*, **18** [10] 278 (1939).
[4] G. W. Brindley and Keith Robinson, "X-ray Studies of Halloysite and Metahalloysite: I, Structure of Metahalloysite, an Example of Random Layer Lattice," *Mineralog. Mag.*, **28** [203] 393–406 (1948).

[5] B. E. Warren, "Structure of Tremolite, $H_2Ca_2Mg_5(SiO_3)_8$," *Z. Krist.*, **72**, 42–57 (1929); *Ceram. Abstr.*, **9** [6] 466 (1930).
[6] J. Zussman, "Crystal Structure of an Actinolite," *Acta Cryst.*, **8** [6] 301–308 (1955).
[7] E. J. W. Whittaker, "Structure of Bolivian Crocidolite," *Acta Cryst.*, **2** [5] 312–17 (1949).
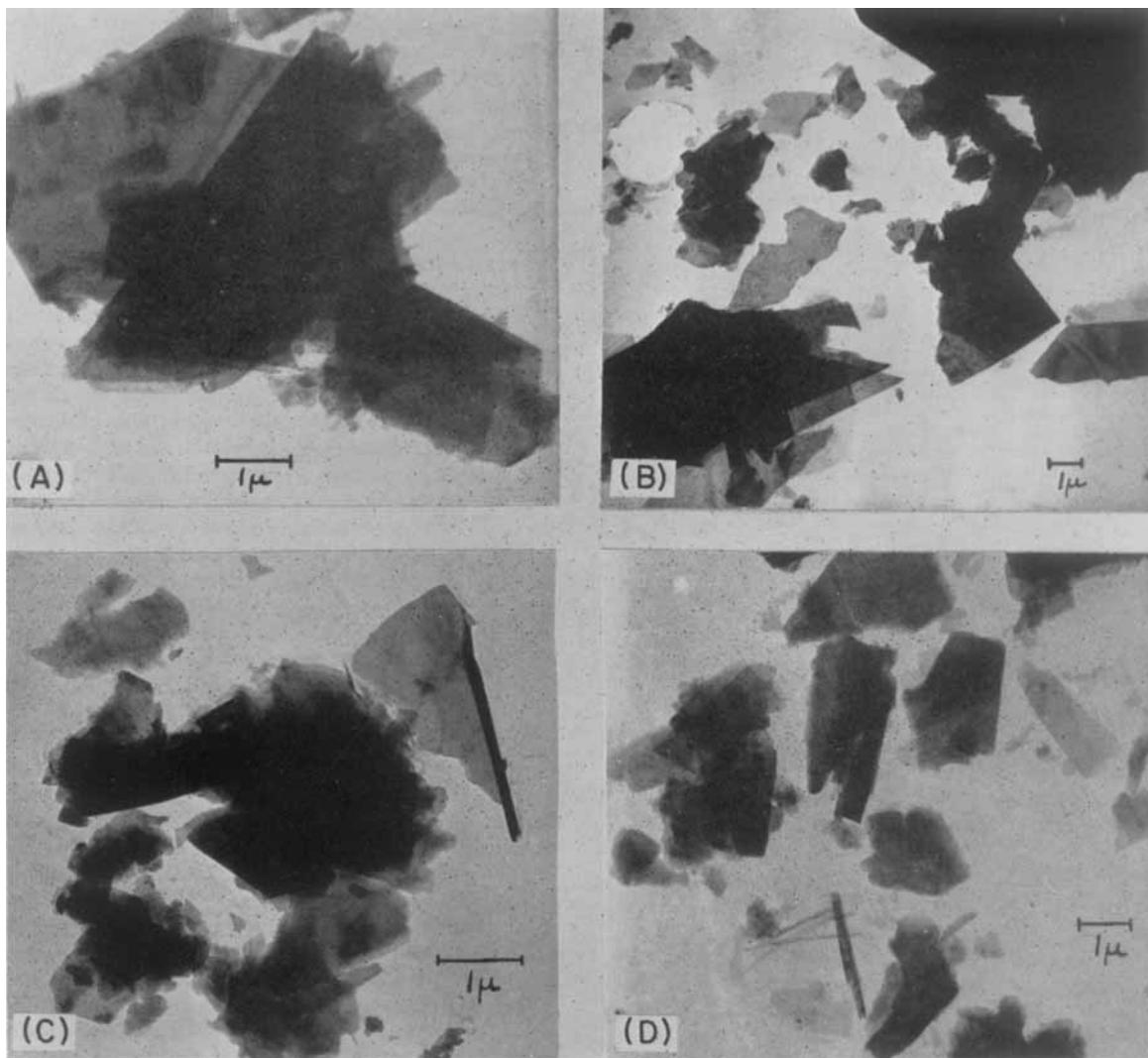
Fig. 2.   Electron micrographs of (A) foliated talc, Harford County, Maryland (No. 11462–5), (B) hard soapstone-like talc, Providence, Rhode Island (No. 11463–2), (C) hard white-gray talc, Alabama (No. 11462–3), and (D) California talc (No. 11461–5).

Table II.   Unit-Cell Parameters of Tremolite and Related Minerals (a.u.)*

	Tremolite (Warren)	Crocidolite (Whittaker)†	Tremolite (present writers)	Actinolite (Zussman)‡
a	9.80	9.89	9.89	9.89
b	17.84	17.95	18.02	18.14
c	5.27	5.31	5.27	5.31
β	73° 58′	72° 30′	73° 58′	105° 48′ (74° 12′)

* Warren values (footnote 5) converted from kX units to angstrom units by the factor 1.002.
† Footnote 7.
‡ Footnote 6.

smallest of the three." The new measurements (see Table II) now place tremolite in an intermediate position, which is more reasonable.

III.   Hand-Specimen Morphology and Electron Micrographs of Talcs

In hand specimens, talcs can be classified broadly into foliated, laminated, massive, and fibrous materials. Among the samples available for this study, the majority were in the massive category. They varied in color from white, through various tints of gray and green, to one sample which was a very dark green and almost black. The majority had the softness and "greasy" feel attributed to talc, but some were of a hard, rather coarse texture.

Apart from the fibrous materials, the various talcs examined showed no marked correlation between hand-specimen characteristics and those seen in the electron microscope. The layer-type crystal structure of talc would lead one to expect platy forms with hexagonal outlines, or at least some "hexagonal" angles, in the electron micrographs. In preparing samples, apart from the soft unconsolidated materials, it was necessary to grind the specimens with pestle and mortar so that in many cases it is essentially fractured particles which are studied by this method; this might account for the irregular outlines obtained in several instances.

The results are illustrated in Figs. 2 and 3. Figure 2 shows the kind of micrographs most commonly obtained. Figure 2(A) is a foliated talc from Harford County, Maryland. The material is platy, and well-developed hexagonal outlines are obtained; it is evident that grinding this material does not preclude hexagonal forms being observed. Figures 2(B), (C), and (D) were obtained respectively from a hard soapstone-like material from Providence, Rhode Island, a
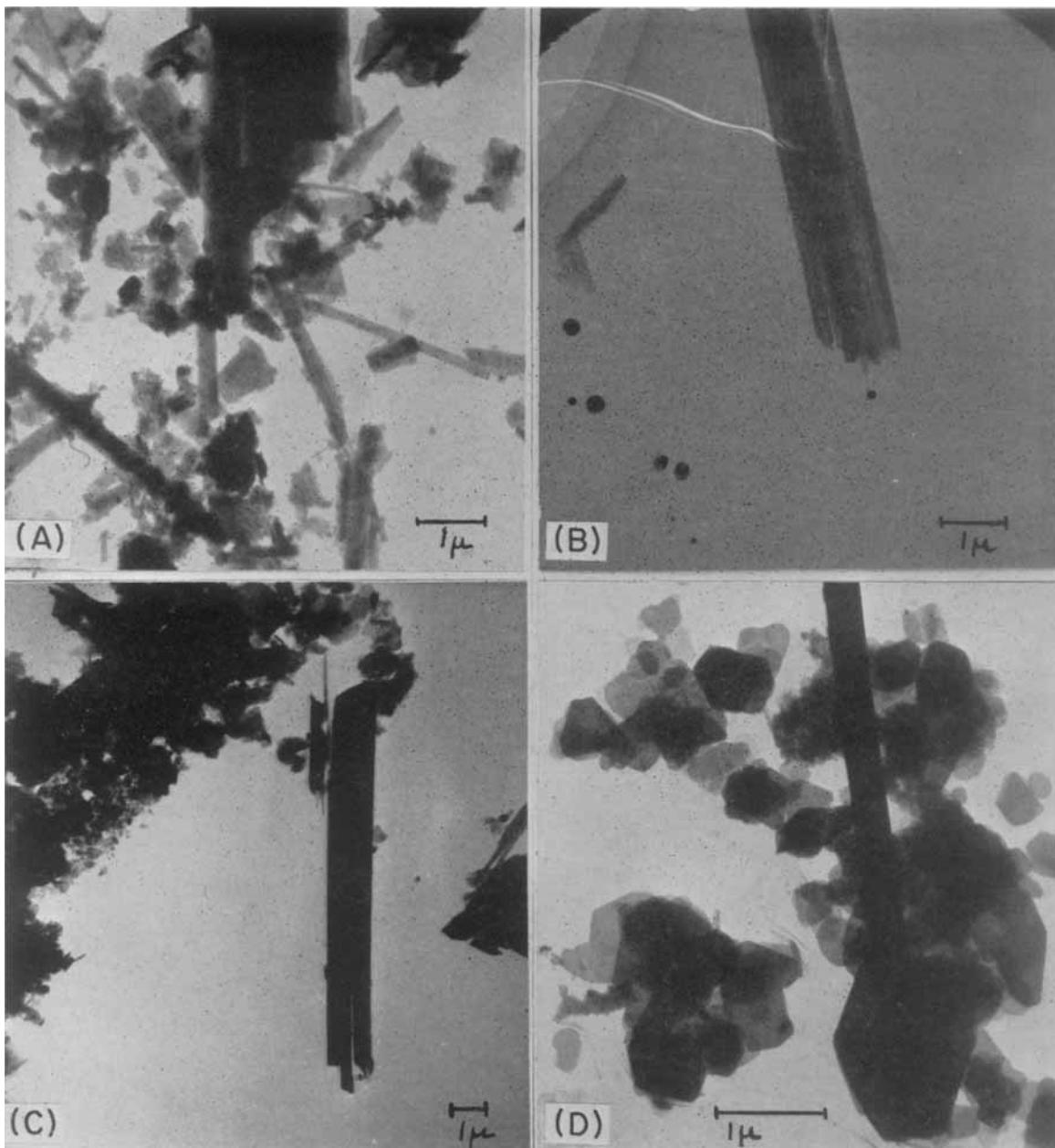
Fig. 3. Electron micrographs of (A) fibrous talc, St. Lawrence County, New York (No. 11461–2), (B) composite talc-tremolite fiber from California talc (No. 11587–4), (C) split fibers and platy debris in California talc (No. 11463–1), and (D) synthetic talc with chrysotile (?) fiber (No. 11460–3).

hard white-gray talc from Alabama, and a white semihard talc from California. Figure 2(B) shows angular fragments with sharp, straight edges, with a ribbonlike fragment also seen. Figure 2(C) shows very irregular particles with many thin plates curling at the edges. Figure 2(D) shows irregular forms with some lathlike particles. Hexagonal forms are almost absent from Figs. 2(B), (C), and (D), although one hexagonal plate is visible in 2(C).

Figure 3(A) is characteristic of many fibrous talcs; the particular specimen shown came from St. Lawrence County, New York. Long lathlike fibers and fine platy debris are seen. Selected-area electron diffraction studies have shown that the platy material is talc, and the fibers are partly talc and partly tremolite. Figure 3(B) shows more clearly one indi-

vidual fiber which has a composite appearance. In this figure and also in Fig. 3(C) the fibers appear to be split lengthwise.

In Fig. 3(D) is shown a hydrothermally prepared synthetic talc. The long fiber is probably chrysotile. Platy crystals with hexagonal outlines are characteristic of the synthetic material but have been witnessed only rarely in micrographs of natural materials.

IV. Electron Diffraction Data for Talc-Tremolite Intergrowths

Electron diffraction patterns of fibers of the kind illustrated in Figs. 3(A), (B), and (C) prove that the fibers consist of very well oriented intergrowths of talc and tremolite.
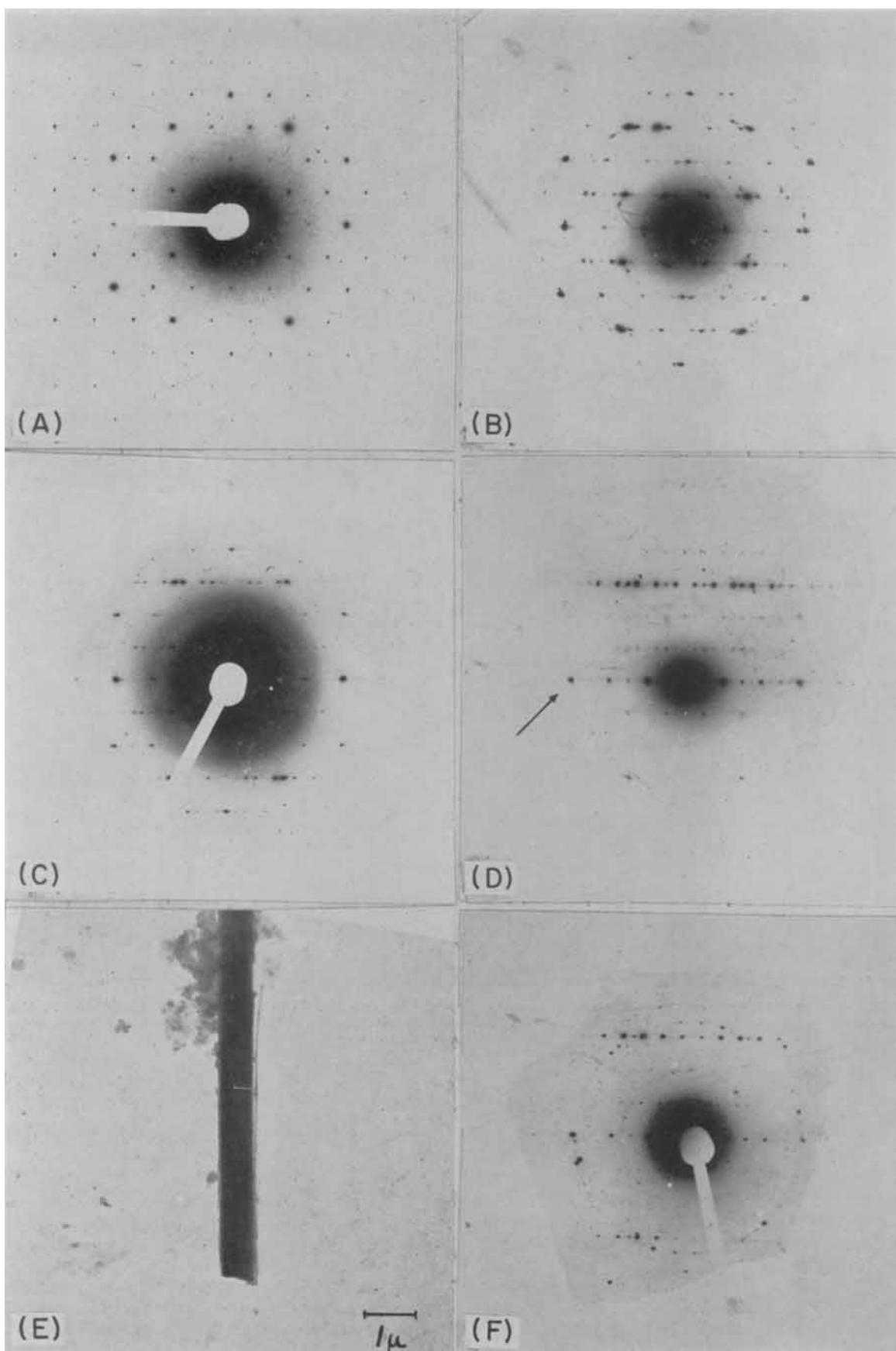
Fig. 4.   Electron diffraction diagrams of talc and of composite fibers of talc and tremolite.   (A) Single crystal of Manchurian talc (No. 11588–3), (B) single fiber from St. Lawrence County, New York (No. 11798–1), (C) single fiber from St. Lawrence County, New York (No. 11475–1), (D) single fiber from St. Lawrence County, New York (No. 11798–5), (E) electron micrograph of fiber which gave the mixed talc-tremolite pattern in (D) (fiber has the same orientation in both diagrams) (No. 11798–4), and (F) single fiber from St. Lawrence County, New York (No. 11589–1).
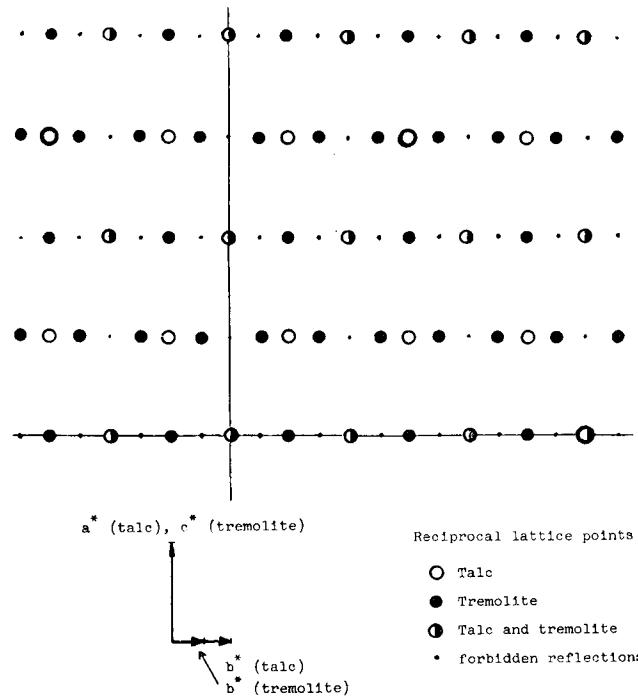
Fig. 5.   Schematic diagram showing superposition of a*b* net of talc and c*b* net of tremolite.   Diagram is idealized in that b* (tremolite) is taken to be exactly (¹/₂)b* (talc).

Fig. 6.   Schematic representations of the structures of talc projected on the bc plane and of tremolite projected on the ab plane.   Diagrams are limited to showing the Si–O networks and the cations Mg and Ca.

Figures 4(*B*), (*C*), (*D*), and (*F*) reproduce four of these mixed diffraction patterns.   Figure 4(*A*) shows an electron diffraction pattern of a platy talc crystal with a well-defined hexagonal arrangement of the spots.   Using Fig. 4(*A*) as a key to the talc reflections, one can easily distinguish the corresponding reflections in Figs. 4(*B*), (*C*), and (*D*); where there appear to be groups of three reflections, the center one corresponds to talc.   The intensity of the talc reflections diminishes from Fig. 4(*B*) to 4(*F*), with 4(*F*) predominantly tremolite.   Figure 4(*E*) shows the individual fiber used for the diagram 4(*D*) *in the same orientation*.

The fact that the combined diffraction patterns have the appearance of a single pattern is a consequence of (*a*) simple relations between the dimensions of the two unit cells and (*b*) certain directional relations between the two components. The unit-cell dimensions of the two structures are as follows:

Talc:

$$a\ 5.29,\ b\ 9.16,\ c\ 18.95\ \text{a.u.},\ \beta\ =\ 99°30' \qquad (1)$$

Tremolite:

$$c\ 5.27,\ b\ 18.02,\ a\ 9.89\ \text{a.u.},\ \beta\ =\ 73°58' \qquad (2)$$

$$c\ 5.27_5,\ b\ 18.05,\ a\ 9.91\ \text{a.u.},\ \beta\ =\ 106°\ 13' \qquad (3)$$
$$73°\ 47'$$

(1) and (2) measured by present writers;   (3), J. Zussman, private communication.

The spacing corresponding to the layer line separation in the electron diffraction diagrams is about 5.3 a.u., corresponding to the *a* of talc and the *c* of tremolite.   The spots along the layer lines correspond to *b* of talc and *b* of tremolite, which are almost, but not exactly, in the ratio 1:2.   Consequently the combined spot sequences are not strictly regular along the layer lines and this is well shown by the threefold groups of spots in Fig. 4(*D*).   Some of the higher-order spots show a splitting of nearly superposed reflections; an example is marked in Fig. 4(*D*).

A general interpretation of the diffraction patterns can be obtained on the basis that the *hk*0 reciprocal net of talc and the 0*kl* reciprocal net of tremolite referred to the body-centered unit cell of Warren[5] (1929) are superimposed.   The
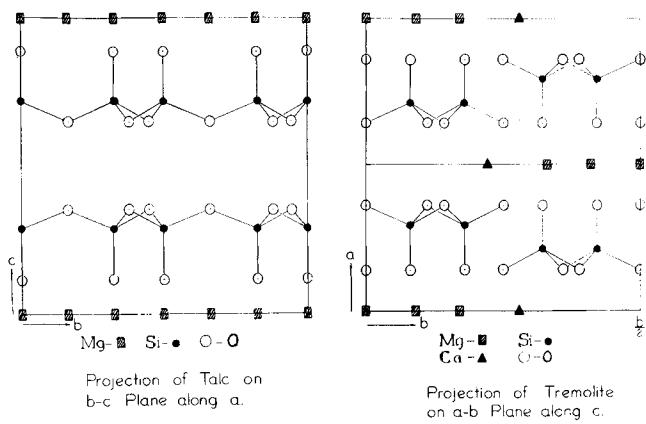
situation is depicted in Fig. 5 where the open circles show (*hk*0) reflections of talc for which (*h* + *k*) is even; the black circles show the (0*kl*) reflections of tremolite, and since (*h* + *k* + *l*) must be even and *h* is zero, then (*k* + *l*) must be even.   Since the *b** parameter of tremolite is about half that of talc, the combined distribution is that given in Fig. 5. The threefold groups on the odd-order "layer" lines arise from the two components separately, each talc reflection being flanked on either side by a tremolite reflection.   Superposition of reflections occurs on the even-order layer lines.

The electron diffraction patterns thus prove that the fibers seen in the electron micrographs are composite fibers containing varying proportions of talc and tremolite, and that there is a well-defined orientational relation between the two minerals.

V.   The Talc-Tremolite Association

The results described in the previous section suggest that each composite fiber represents a partial transformation of one mineral into the other, probably tremolite transformed into talc, with the structural relation between them still preserved.

Figure 6 shows schematically the two structures placed side by side with the observed orientational relations.   The *c* axis (fiber axis) of tremolite and the *a* axis of talc are parallel to one another and normal to the plane of the diagram; the *b* axes of the two structures are parallel.   The two remaining axes are not strictly parallel, since the structures are monoclinic with β (talc) = 99° 30' and β (tremolite) = 106° 13' or the complementary angle, 73° 47'.   Therefore *c* (talc) and *a* (tremolite) are inclined to the plane of the diagram by about 10° and 16° respectively, and the dimensions shown in Fig. 6 are the projected dimensions, *c* sin β and *a* sin β respectively.

It seems likely that tremolite is converted to talc by a rearrangement of the silicon-oxygen groups and a replacement of the Ca ions (for which there are no positions in the talc structure) by Mg ions.   The oxygen layers in the two structures are very similar, but whereas in talc the Si–O tetrahedra in any one sheet point in the *same* direction, the corresponding tetrahedra in tremolite point in *opposite* directions.

With small migrations of the Si ions to invert half the tetrahedra in tremolite, removal of the Ca ions, and consolidation of the Mg ions, the tremolite structure is transformed into the talc structure.   The migration of the Si ions suffices to link the chains of tremolite into the sheets of talc.   The structural rearrangement involved is rather small and is such that a high degree of orientational alignment between the two structures would be expected.

Table III.   Basal Spacing Measurements for Some Natural and Synthetic Talcs

(a)   Natural talcs

	$2\theta°$ (006)
Manchuria talc	28.65*
California talc	28.62*
Alabama talc	28.65*
Bare Hills, Maryland, talc	28.60*

(b)   Synthetic talcs

Mole ratio MgO-Al$_2$O$_3$-SiO$_2$	2θ (006)	Time (days)	Temp. (°C.)	Impurities
3-0-4	28.66*	8	650	
3-0-4	28.66‡	3	760	
3-0-4	28.70†	8	674	
3-0-4	28.60†	1	700	
17-3-20	28.70*	6	680	Al-S
17-3-20	28.80†	2	760	E
9-1-8	28.70†	6	680	Ch
9-1-8	28.75*	3	748	
5-1-7	28.85*	2	760	S
5-1-7	28.95*	6	680	C
2-1-3	28.83*	6	680	C, S, M
2-1-3	28.85*	2	760	C, M

* Diffractometer record taken at $^1/_4°$ 2θ per minute.
† Diffractometer record taken at $1°$ 2θ per minute.
‡ Film measurement.
IMPURITIES: Al-S, Al-serpentine; E, enstatite; Ch, chlorite; S, spinel; C, cordierite; M, mullite.

The chemical relation between the two minerals can be expressed as follows:

$$Ca_2Mg_5Si_8O_{22}(OH)_2 + Mg(OH)_2 - 2CaO = 2[Mg_3Si_4O_{10}(OH)_2]$$
tremolite   talc
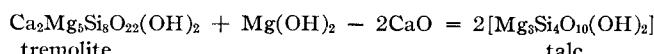
VI.   Synthetic Talcs

Synthetic talcs have been studied by Yoder[8] (1952), who reported (p. 574) that "In compositions in which alumina is present, the unit cell of talc shrinks measurably in the c-dimension. . . . . On this evidence, there is a basis for concluding that talc does take limited amounts of aluminum into its structure. The alumina content of some natural talc is as high as 3.75 per cent (Wells, 1937), and in one specimen analyzed in 1851 the alumina was 4.7 per cent (Scheerer)."

Since no quantitative data were reported by Yoder on the magnitude of the lattice parameter changes, it was thought desirable to explore this question more fully. L. Ramspott and M. S. Crowley working with Rustum Roy prepared a series of compositions using various initial proportions of MgO, Al$_2$O$_3$, and SiO$_2$ in order to obtain talcs of the type

$$(Mg_{3-x}Al_x)(Si_{4-x}Al_x)O_{10}(OH)_2$$
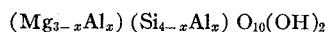
The mole ratios are listed in Table III and correspond to the following values of x: 17-3-20, $x = 0.3$; 9-1-8, $x = 0.45$; 5-1-7, $x = 0.5$; 2-1-3, $x = 1$. These compositions were reacted in gold envelopes and also in sealed gold tubes at 15,000 lb. per sq. in. and various temperatures.

X-ray powder data were obtained by diffractometer traces and from film measurements. They confirm Yoder's evidence for solid solubility of aluminum in talc but are inconclusive as to the extent of the solubility; it is clearly less than the mole ratio 17-3-20 since this composition already shows the presence of a second phase. Data for the 006 reflection are listed in Table III.

For natural talcs and for synthetic talcs prepared from MgO and SiO$_2$, there is good agreement between the 2θ (006) values, and the mean value, $28.64° \pm 0.03$, corresponds to $d(001) = 18.70_1$ a.u.

Synthetic talcs prepared in the presence of Al$_2$O$_3$ give an average value for 2θ (006) of $28.81° \pm 0.07$ corresponding to $d(001) = 18.59_3$ a.u. If these talcs are saturated with Al ions (as the presence of aluminum-containing impurities suggests), then a constant value for $d(001)$ would be expected, but a closer inspection of the data, and more particularly of the data obtained with slow recording, suggests a small but progressive change of 2θ with aluminum content. This is difficult to understand, and more detailed work will be required to establish the finer points of these results. It seems to be well established, however, that aluminum can enter the talc lattice to a small extent with a maximum shrinkage of $d(001)$ by about 0.6%.

Changes in the a and b parameters are smaller than in $d(001)$. The b parameter *may increase* by about 0.1 or 0.2%, and if this is attributed wholly to an AlO$_4$ tetrahedron being about 10% larger in linear dimensions than a SiO$_4$ tetrahedron, then a replacement of 1 in 100 Si by Al ions would give a 0.1% increase in b. A corresponding number of Al ions would replace Mg for electrical neutrality. Thus a 0.1% increase in b corresponds to a Si/Al atom ratio of 50:1 and a 0.2% increase in b to an atom ratio of 25:1. If one takes the figure quoted by Yoder of 3.75% Al$_2$O$_3$ in a talc containing about 60 weight % SiO$_2$, the Si/Al atom ratio is about 15:1.

On the basis of the present evidence it thus appears that a small proportion of Al ions may enter the talc lattice, contracting $d(001)$ by about 0.6%, and producing a doubtful expansion of b by about 0.1 to 0.2%. The proportion of Si to Al ions is of the order of 15:1 to 25:1.

VII.   Conclusions

An X-ray diffraction survey of about forty specimens of talc has revealed variations in degree of crystallinity and of orientation of the mineral but has provided no evidence for polymorphic varieties. Single-crystal data have confirmed the two-layer monoclinic cell described by Gruner and by Hendricks.

Electron micrographs have shown that talc particles exhibit a variety of platy forms, and fibrous forms also exist. Single-crystal electron diffraction patterns have proved that the fibrous particles consist of a close association of talc and tremolite with a simple orientational relation between the components. It is shown that this relation can be interpreted in terms of a simple structural transformation from tremolite to talc.

The X-ray study of pure synthetic talcs, and of talc prepared in the presence of aluminum, suggests that a small percentage of Al ions may enter the talc structure, the Al-Si ratio probably being no higher than about 1:25 or 1:15; the latter corresponds to about 3.7 weight % of alumina.

POSTSCRIPT: Since this paper was written, a further study of tremolite has been made by Zussman (*Acta Cryst.*, **12** [4] 309–12 (1959)) in which he gives unit-cell parameters very similar to those found in the present study. He also emphasizes the very close and somewhat confusing relation between two possible unit cells (C-face-centered and body-centered) which must be taken into account in precise comparisons of different data.

[8] H. S. Yoder, Jr., "The MgO–Al$_2$O$_3$–SiO$_2$–H$_2$O System and Related Metamorphic Facies," *Am. J. Sci.*, **Bowen Volume**, Part 2, 569–627 (1952).

January 1960 *Structural Study of Talc and Talc-Tremolite Relations* 41

APPENDIX

Indexed X-Ray Powder Data for Talc and Tremolite

X-Ray Powder Data for Talc*

hkl	Gruner d, calc	Gruner d, obs (I)	Present results d, calc	Present results d, obs (I)
002	9.278	8.96 (5)	9.349	9.34 (>100)†
004	4.639⎫		4.674	4.66 (90)†
020	4.559⎭	4.58 (3)	4.578⎫	
11$\bar1$	4.540		4.562⎭	4.55 (30)
110	4.507		4.526	
021	4.427		4.449	
11$\bar2$	4.318		4.344	
111	4.235		4.251	
022	4.092		4.112	
11$\bar3$	3.937⎫	3.83 (1B)	3.964	
112	3.833⎭		3.847	
023	3.670		3.690	
11$\bar4$	3.508		3.534	3.510 (4)?
113	3.406	3.38 (3)	3.420	3.430 VWCr
006	3.092	3.066 (10)	3.118	3.116 (>100)†
025			2.896	2.892 VWCr
130	2.622		2.634	
20$\bar2$	2.618		2.630	2.629 (12)
200	2.593		2.602	
13$\bar2$	2.583	2.565 (1B)	2.596	2.595 (28)
132	2.467⎫	2.454 (5)	2.478⎫	2.476 (65)
20$\bar4$	2.452⎭		2.467⎭	
202	2.392		2.399	
13$\bar4$	2.374		2.388	
008	2.320	2.317 (1)	2.337	2.335 (15)†
134	2.201⎫	2.192 (2B)	2.211	2.212 (20)
20$\bar6$	2.182⎭		2.198	2.196 (10Nr)
222	2.118		2.126	
204	2.112		2.120	2.122 (8Nr)
13$\bar6$	2.093	2.085 (1B)	2.107	2.103 (20)
136	1.919	1.924 (1/2)	1.928	1.930 (6B)
20$\bar8$	1.901		1.890	
00, 10	1.856	1.854 (3)	1.870	1.870 (40)†
206	1.837		1.843	
13$\bar8$	1.819		1.831	
24$\bar2$			1.727	1.725
24$\bar4$			1.678⎫	1.682 (20B)
138	1.666	1.667 (3B)	1.675⎭	
20, $\bar{10}$	1.650	1.655 (1-2)	1.665	
208	1.596	1.635 (1B)	1.603	
13, $\bar{10}$	1.582		1.593	
00, 12	1.547	1.547 (2)	1.558	1.557 (20)†
060	1.520⎫	1.518 (4)	1.526⎫	1.527 (40)
33$\bar2$	1.520⎭		1.526⎭	
228			1.513	
330	1.502⎫	1.502 (1)	1.508	1.509 (10)
062	1.500⎭		1.506	
33$\bar4$	1.497		1.505	
13, 10	1.456	1.464 (1)	1.464	1.460 (8B)
064			1.455	
20, $\bar{12}$	1.443	1.449 (1/2)	1.451	
20, 10	1.399	1.408 (2)	1.405	1.406 (15Nr)
13, $\bar{12}$	1.387⎫	1.378 (3B)	1.397	1.394 (20Nr)
334	1.370⎭		1.375	
066	1.364		1.371	
33$\bar8$	1.358		1.367	
00, 14	1.326	1.330 (1-2)	1.336	1.336 (15)†
26$\bar2$	1.314	1.316 (1)	1.320	
260	1.312		1.317	1.318 (10)
40$\bar4$	1.310		1.315	
400	1.297⎫	1.292 (2B)	1.301	
26$\bar4$	1.292⎭		1.298	1.297 (10B)
13, 12	1.284		1.291	
262	1.283		1.288	
20, $\bar{14}$	1.274		1.284	
068	1.272		1.278	
33, $\bar{10}$	1.265	1.265 (1/2)	1.274	1.269 (10)
20, 12	1.236		1.243	
264	1.233	1.232 (1)	1.238	
13, $\bar{14}$	1.227		1.237	
00, 16	1.162	1.167 (1/2)	1.169	1.169 (5)†

* *d* in angstrom units; *I* = intensity; B = broad; VWCr = very weak reflection recorded on film with CrK radiation; Nr = not resolved.

† Enhanced by orientation.

(1) Talc

Indexed powder data for talc by Gruner and by the present writers are tabulated. Differences in the calculated data arise from the different unit-cell parameters, which are listed in Table I. The reflection intensities were estimated visually by Gruner and were taken from diffractometer recordings in the present work.

(2) Tremolite

X-ray powder data obtained with a Philips high-angle diffractometer and filtered CuKα radiation (λ 1.5418) are tabulated for three specimens of the mineral from sources listed in the table. The calculated lattice spacings are complete down to *d* 2.252 a.u.; for smaller spacings the number of possible reflections is too great for a complete listing but the probable indices of the observed reflections are given. The minerals were finely powdered by pestle and mortar, and were packed with a minimum of pressure. Nevertheless, there are some marked differences between the intensities from different specimens, and preferential orientation probably has a strong influence. The observed spacings agree well with each other and with the calculated values.

X-Ray Powder Data for Tremolite*

hkl	d, calc	d(I), obs Specimen (1)	Specimen (2)	Specimen (3)
020	9.010	8.93 (15)	8.98 (15)	8.98 (10)
110	8.407	8.38 (100)	8.38 (100)	8.38 (100)
130	5.077⎫	5.07 (15)	5.07 (15)	5.08 (15)
101	5.061⎭			
011	4.875	4.87 (10)	4.87 (10)	4.87 (5)
200	4.751	4.74 (20)	4.76 (20)	4.75 (50)
040	4.504	4.51 (20)	4.51 (20)	4.51 (10)
121	4.413			
220	4.203	4.20 (60)	4.20 (35)	4.20 (55)
10$\bar1$	4.046			
211	3.943			
031	3.872	3.875 (10)	3.870 (15)	3.875 (10)
12$\bar1$	3.690			
150	3.369⎫	3.376 (35)	3.376 (40)	3.376 (20)
141	3.364⎭			
231	3.352			
240	3.269	3.267 (75)	3.268 (75)	3.272 (75)
310	3.120	3.116 (>100)	3.121 (>100)	3.121 (>100)
301	3.078			
21$\bar1$	3.037⎫	3.028 (70)	3.028 (10)	
14$\bar1$	3.010⎭			
060	3.003			
051	2.937	2.931 (35)	2.938 (40)	2.935 (35)
321	2.913			
330	2.802	2.801 (70)	2.805 (45)	2.804 (60)
32$\bar1$	2.742	2.730 (15)	2.730 (15)	2.730 (20)
251	2.690	2.702 (70)	2.705 (90)	2.702 (60)
341	2.649			
112	2.599⎫	2.590 (20)	2.592 (30)	2.585 (20)
161	2.583⎭			

Specimen (1): A whitish-gray massive material with intergrown fibrous crystals, West Redding, Connecticut.
Specimen (2): White radiating masses of fine fibers, St. Gotthard, Switzerland.
Specimen (3): Finely fibrous material, white (and in part a greenish tint), St. Gotthard, Switzerland.

* Calculated data for body-centered monoclinic cell with *a* 9.89, *b* 18.02, *c* 5.27 a.u., β 73°58′. *d* in angstrom units; *I* = intensity; B = broad.

X-Ray Powder Data for Tremolite (continued)

hkl	d, calc	Specimen (1)	Specimen (2)	Specimen (3)
			d(I), obs	
260	2.539			
002	2.532⎫			
202	2.530⎭	2.529 (30)	2.529 (40)	2.529 (15)
170	2.495	2.488 (4)		
022	2.438			
222	2.437			
30$\bar{1}$	2.414			
16$\bar{1}$	2.412			
132	2.407	2.407 (7)	2.407 (8)	2.407 (6)
411	2.390⎫			
350	2.380⎬	2.380 (30)	2.380 (30)	2.380 (25)
400	2.376⎭			
25$\bar{1}$	2.342	2.335 (30)	2.335 (30)	2.335 (30)
32$\bar{1}$	2.331	2.323 (15)	2.321 (40)	2.321 (30)
420	2.298⎫			
071	2.295⎭	2.295 (10)	2.298 (12)	2.301 (15)
11$\bar{2}$	2.281			
312	2.280	2.273 (20)	2.273 (15)	2.273 (12)
080	2.252			
		Partial listing of calculated data		
042	2.207⎫			
242	2.206⎭	2.204 (5)	2.206 (5)	2.206 (5)
34$\bar{1}$	2.189	2.178 (8)	2.181 (5)	2.181 (3)
271	2.171⎫			
361	2.150⎭	2.161 (35)	2.163 (35)	2.161 (35)
181	2.058⎫			
280	2.035⎭	2.042 (18)	2.042 (18)	2.042 (10)
20$\bar{2}$	2.023			
402	2.021	2.014 (25)	2.015 (45)	2.014 (25)
451	2.004⎫			
370	1.998⎭	1.998 (20)	2.002 (15)	2.002 (20)

X-Ray Powder Data for Tremolite (concluded)

hkl	d, calc	Specimen (1)	Specimen (2)	Specimen (3)
			d(I), obs	
18$\bar{1}$	1.968⎫			
190	1.959⎭	1.965 (7)	1.963 (6)	1.963 (8)
352	1.937	1.926 (4)	1.929 (5)	1.926 (7)
510	1.891	1.892 (35)	1.892 (50)	1.892 (100)
460, 43$\bar{1}$	1.864⎫			
091	1.862⎭	1.862 (8)	1.864 (15)	1.864 (10)
530	1.812	1.812 (20)	1.814 (15)	1.812 (45)
0, 10, 0	1.802	1.802 (4)		
103	1.744	1.746 (5)	1.746 (5)	1.749 (5)
303	1.687⎫			
082	1.683⎬	1.684 (10)	1.686 (10)	1.684 (8)
282	1.682⎭			
1, 10, $\bar{1}$	1.646	1.649 (35)	1.649 (40)	1.650 (35)
480	1.635⎫			
611	1.634⎭	1.637 (10)	1.639 (10)	1.639 (20)
52$\bar{1}$	1.616	1.617 (20)	1.617 (12)	1.618 (12)
600	1.585	1.585 (10)	1.585 (10)	1.585 (80)
631	1.583	1.578 (7)	1.579 (15)	
3, 10, 1	1.555	1.556 (7B)	1.556 (7B)	1.558 (12B)
570	1.529	1.532 (8B)	1.532 (15)	1.532 (12)
392	1.510	1.513 (8)	1.511 (12)	1.512 (5)
0, 12, 0	1.501	1.501 (15)	1.501 (20)	1.503 (20)
2, 10, 2	1.468⎫			
21$\bar{3}$	1.467⎭	1.467 (5)	1.468 (6)	1.469 (5)
3, 11, 0	1.455⎫			
37$\bar{2}$, 453	1.454⎭	1.455 (7)	1.451 (8)	1.459 (5)
4, 10, 0	1.436	1.438 (50)	1.439 (55)	1.437 (50)
Three strongest reflections		3.116 (>100)	3.121 (>100)	3.121 (>100)
		8.38 (100)	8.38 (100)	8.38 (100)
		3.267 (75)	2.705 (90)	1.892 (100)

An Optical Study of Talc-Tremolite Relations

by HAROLD D. WRIGHT

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An optical study of talc-tremolite from Fullerville, St. Lawrence County, New York, confirmed the crystallographic orientation determined by Stemple and Brindley. Both minerals exhibit normal optic properties. The optic orientation of talc given in standard references appears to be in error.

A N optical study was made of a specimen of talc-tremolite rock from Fullerville, St. Lawrence County, New York, used in the X-ray study by Stemple and Brindley.[1] The purpose was to determine the optic constants of each mineral and compare these with published data, and to obtain information on the textural and optical relation of the two minerals. In particular, a search was made for evidence of direct alteration of tremolite to talc, whereby optic orientation might provide additional evidence on the crystallographic relation of the alteration product to the host.

Talc was found to comprise more than 90% of the material examined under the microscope. All of it is in the form of fibrous plates or laths parallel to the basal cleavage, occurring individually or in aggregates. The straight sides of the laths have the appearance of a second cleavage but generally have been attributed to inheritance of the fibrous structure of tremolite. The laths produce centered acute bisectrix interference figures with the trace (γ) of the optic plane parallel to the long dimension. The optical data obtained on this talc are summarized in Table I. All the data agree with published values[2, 3] except for the optic orientation, which is

[1] I. S. Stemple and G. W. Brindley, "A Structural Study of Talc and Talc-Tremolite Relations," this issue, pp. 34–42.

[2] A. F. Rogers and P. F. Kerr, Optical Mineralogy, 2d ed., p. 350. McGraw-Hill Book Co., Inc., New York, 1942.

[3] A. N. Winchell, with Horace Winchell, Elements of Optical Mineralogy: II, Descriptions of Minerals, 4th ed., p. 364. John Wiley & Sons, Inc., New York, 1951. 551 pp.; Ceram. Abstr., 1952, May, p. 102g.

Exhibit 32

Discussion on the Genesis of Longsheng Talc Mine in Guangxi Province

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Li Yuya

I. Overview of Ore Deposit Geology

Longsheng talc mine in Guangxi Province is the largest talc treasury in South China, and the ore deposit occurs in the east wing of Sanmen complex overturned anticline (See Figure 1), strictly controlled by NNE regional compressive fracture structure (Metallogenic structure) as well as dolomite marble ($ptbh^5$) and spilite ($ptbh^4$). According to the linear distribution features of talc ore occurrence as well as the dependence relationship with the NNE compressive fracture, the talc mine can be roughly divided into two metallogenic belts. The first metallogenic belt, controlled by F_1 fracture, is mainly comprised of Guping Mining District, Lower Jizhua Mining District and Tongzishan Mining District. This metallogenic belt having a length of about 8km is the most important talc base in this zone. The second metallogenic belt, controlled by F_3 fracture, is mainly comprised of Middle Jizhua Mining District and Gutang Mining District. This metallogenic belt having a total length of 12km is only second to the first metallogenic belt in the industrial significance. The metallogenic geological conditions of each mining district are basically similar, and the scale of the Lower Jizhua Mining District is largest.
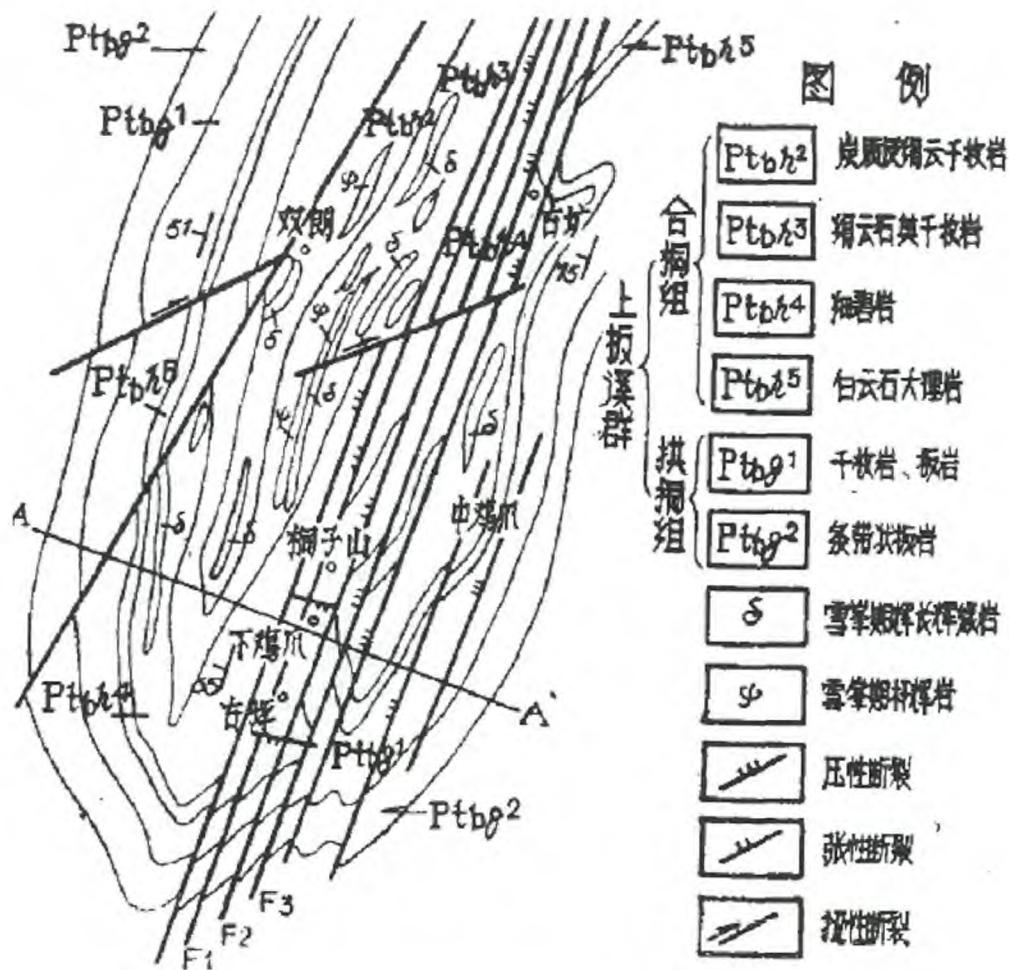
Figure 1 Regional Geological Map of Longsheng Talc Mine

图例	Legend
上板溪群	Upper Banxi Group
合桐组	Hetong Formation
炭质绢云千枚岩	Carbonaceous sericite phyllite
绢云石英千枚岩	Sericite quartz phyllite
细碧岩	Spilite
白云石大理岩	Dolomite marble
拱桐组	Gongtong Formation
千枚岩、板岩	Phyllite and slate
条带状板岩	Stripped slate

雪峰期辉长辉绿岩	Gabbro-diabase in Xuefeng period
雪峰期杆辉岩	Olivine-bearing pyroxenite in Xuefeng period
压性断裂	Compressive fracture
张性断裂	Tensional fracture
扭性断裂	Torsional fracture
桐子山	Tongzishan
下鸡爪	Lower Jizhua
中鸡爪	Middle Jizhua
古坪	Guping
双朗	Shuanglang
古塘	Gutang

In this zone, the talc ores occur in the dolomite marble (ptbh^5). The ore body is laminar or lenticular, and the occurrence is roughly the same as the surrounding rocks, inclined to NWW with an inclination angle of 35-65°. The dolomite marble remains are always sandwiched in the talc ores and the talc ores are clearly bounded with the surrounding rocks and horse stones. The common paragenetic mineral is quartz stone and very few calcite clumps are occasionally seen.

Ore quality: generally grayish white-light green, occasionally grayish green, containing 60-62% SiO_2, 30-31% MgO and 0.4-1.6% Fe_2O_3 (generally less than 0.8%). According to the statistics of Guping Mining District and Lower Jizhua Mining District, the content of first-grade ores accounts for 70-75% and the quality is good.

II. Relations between Regional Geology and Mineralization

1. Relations between Formation and Mineralization

The exposed regional formations mainly include the Proterozoic upper Banxi Group, Sinian system and Cambrian system etc. Now the Proterozoic upper Banxi Group is briefly introduced from old to new as follows:

(1) Hetong formation (ptbh)

It is divided into five formations as shown in Figure 1 and Figure 2.

a. ptbh^1: gray-grayish green sericite phyllite and quartz phyllite etc., distributed at the north section of Sanmen complex overturned anticline core (Figure 1 is the south section of anticline) with a thickness of 550m.

b. $ptbh^2$: black gray carbonaceous phyllite and sericite phyllite, exposed at the south section core of Sanmen complex overturned anticline with a thickness of about 200m.

c. $ptbh^3$: grayish green sericite phyllite, slate and siliceous rock, etc. with a thickness of 400m.

d. $ptbh^4$: grayish green spilite sandwiched with grayish green sericite phyllite and siliceous rock with a thickness of 515-861m.

e. $ptbh^5$: thin-medium thick laminar dolomite marble in which the talc ores occur with a thickness of about 200m.

(2) Gongtong formation

a. Lower section of $ptbg^1$: light gray-grayish green sericite quartz phyllite, slate and siliceous rock, etc. with a thickness of 400m.

b. Upper section of $ptbg^2$: stripped slate, phyllite and metasandstone, etc. with a thickness of 150m.

The dolomite marble ($ptbh^5$) is grayish white and medium-fine-grained, containing 18-20% MgO. It is a favorable mother rock for mineralization. In addition, what has an auxiliary relation with mineralization is spilite ($ptbh^4$).

The spilite is greatly developed in this zone, which is a basic rock with submarine eruptive facies and has an obvious pillow-shaped, porous and amygdaloidal structure and a microscopic diabasic structure. The rock is generally altered under the regional metamorphism. The spilite is mainly comprised of soda feldspar (35-45%), tremolite (30-35%), clinozoisite (10-15%) as well as calcite, a small amount of quartz and chlorite. In the east wing of Sanmen complex overturned anticline, when the NNE compressive fracture cuts the spilite, a strong dynamic metamorphic zone is formed in the hanging wall, the primary texture and structure of spilite completely disappear and then the rock is altered into the talcous chlorite schist (containing a large amount of amesite) that has an obvious schistosity structure. The spilite contains 8.14% MgO on average and thus it is a favorable surrounding rock that has an additional effect for mineralization.

2. Relations between Regional Tectonics and Mineralization

The regional tectonics belongs to the Neocathaysian tectonic system. The genesis of ore deposit is closely related to Sanmen complex overturned anticline that has a pinacoidal strike of NE 20-30°, an inclination of NWW, an inclination angle of 60-65°, a length of about 60km and a wing width of 20-25km. This anticline is a closed complex fold that is overturned eastwards and is comprised of two secondary overturned anticlines sandwiched with an overturned syncline. As shown in Figure 2, the formation inclination is NWW, the inclination angle of west wing is 50-60° and the east wing is slightly steep with an inclination angle of 60-70°. In the east wing of this anticline, as the NWW-SEE pressure is highly concentrated, a complex fold belt is formed, the regional longitudinal compressive fracture is greatly developed, and the dynamic metamorphism is so strong to form a series of imbricate fault blocks. In this zone, the talc ore occurrence (ore deposit) is mainly distributed in the NNE compressive fracture zone of the complex anticline's east wing. Although

there is the same favorable formation for mineralization in the west wing of this anticline, as the NNE compressive ore-controlling fracture is not developed and the dynamic metamorphism is weak, the talc ore deposit that has the industrial value is not formed. Therefore, the talc ore is greatly related to the structure of NNE compressive fracture in terms of genesis in this zone.

Figure 2 Regional geological profile map of A-A

3. Relations between Regional Igneous Rock and Mineralization

The exposed magmatic rock in this zone is mainly the diabase with hypabyssal facies (δ), including the gabbro-diabase. A few ultra-basic rocks-olivine pyroxenolite (φ) also exist at the anticlinal core. The above magmatic rocks occur along the formation in a shape of rock bed or dyke, mainly in the $ptbh^1$-$ptbh^4$ formations. It is determined that the absolute age is 837 million years and they were formed in Xuefeng Period in relation to the homologous phase-out of spilite.

The above basic-ultra-basic rocks are far apart from the geologic age of Sanmen complex overturned anticline in Caledonian period as well as NNE compressive fracture and talc mineralization. Meanwhile, after six chemical analysis samples of gabbro-diabase are equally grouped, it is shown through calculation that no SiO_2 is left by taking Zavaritskii's chemical graphic calculation method for rocks. In other words, the basic-ultra-basic magma cannot be separated into the excessive acid hydrothermal solution containing SiO_2. See the following table for more details.

The calculation result Q in the following table is a negative value, showing that SiO_2 is insufficient in the gabbro-diabase and thus a lot of acid hydrothermal solution containing SiO_2 cannot be separated. Through field observation, the quartz vein is scarce near the above rock mass and the silicification of surrounding rocks is weak, so it is further demonstrated that this type of magmatic rock has no genesis relationship with the talc ore.

In addition, in the east wing of Sanmen complex anticline, when the regional compressive fracture cuts such formations as $ptbh^1$-$ptbh^2$ sericite phyllite, slate, sandstone and siliceous rock etc., the

Reference Translation- may contain inconsistencies

stringer-shaped intermediate-acid (quartz diorite) dyke in Caledonian period is occasionally seen. What is worth reflecting on is that this type of dyke is not intruded into the compressive ore-controlling fracture zones F_1 and F_2. According to the 1: 1,000,000 satellite photograph scanned and taken by the 5-7 wave band (MSS 5-7 yellow red- infrared light) of earth resources technology satellite provided by NASA, the sign of concealed intermediate-acid igneous rock mass is not seen in Longsheng area and within the scope of Sanmen complex anticline. But in this photograph, the sign of concealed igneous rock mass is extremely obvious in the other areas. It is estimated that the total content of SiO_2 in two metallogenic belts of this zone and required for silicification of the ore-controlling fracture's surrounding rocks reaches more than 100 million tons. If there is no enormous acid igneous rock mass, a lot of middle-low temperature acid hydrothermal solution source containing SiO_2 cannot be provided for mineralization. In the intermediate-acid dyke as above mentioned, the rock mass is too small to provide a lot of SiO_2 for mineralization. To sum up, it can be thought that the magmatic rock in this zone is unrelated to the genesis of talc ore.

Average component calculation sheet of six gabbro-diabase samples

Oxide	Content (%)	Number of molecules	Characteristic number
SiO_2 50.80	846		$S = 846 + 14 = 860$
TiO_2 1.04	14		$A = (58 + 7) \times 2 = 130$
Al_2O_3 15.11	149		$\therefore Na_2O + K_2O < Al_2O_3$
MgO 7.70	191		$C = 149 - (58 + 7) = 84 \ < CaO$
CaO 5.02	89		$B = FeO' + CaO' + MgO$
Fe_2O_3 0.39	3		$FeO' = FeO + Fe_2O_3 \times 2 + MnO$
FeO 8.44	118		$= 118 + 3 \times 2 + 3 = 127$
MnO 0.19	3		$CaO' = CaO - C = 89 - 84 = 5$
P_2O_5 0.18	1		$B = 127 + 5 + 191 = 323$
Na_2O 3.60	58		$N = A + B + C + S = 1397$
K_2O 0.68	7		$S = \dfrac{860}{1397} \times 100 = 61.56,$ $a = \dfrac{130}{1397} \times 100 = 9.3$ $b = \dfrac{323}{1397} \times 100 = 23.00,$ $C = \dfrac{84}{1397} \times 100 = 6.0$ $Q = S - (3a + 2c + b)$
Total	93.15	1397	$Q = S - (3a + 2c + b)$ $= 61.56 - (3 \times 9.3 + 2 \times 6 + 23)$ $= -1.34$

Reference Translation- may contain inconsistencies

III. Genesis of Ore Deposit

1. Problem Posing

It is generally thought in the metallogenic theory that the dolomite marble is metasomatized by the post-magmatic middle-low temperature acid hydrothermal solution to generate the talc ore, which is expressed according to the following reaction equation:

$$3CaMg(CO_3)_2 + 4SiO_2 + H_2O \longrightarrow Mg_3Si_4O_{10}(OH)_2$$

白云石　　　　　酸性热液　　　　　　滑石

$$+ 3CaCO_3 + 3CO_2 \uparrow$$

方解石
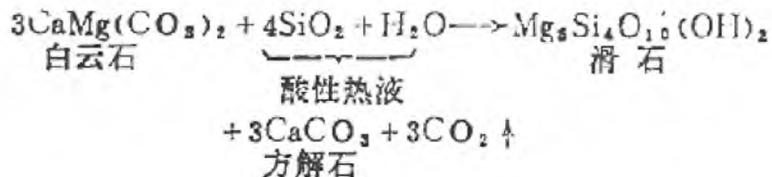
白云石	Dolomite
酸性热液	Acid hydrothermal solution
滑石	Talc
方解石	Calcite

Proven by Johnston and Niggli, in the metasomatism process of solid minerals, the reactant follows the principle of keeping roughly equal in volume with the resultant, namely the law of equivoluminal metasomatism. It is thought by F.J Turner and other scholars that when a kind of metamorphic rock assemblage is generated from mother rock and there is no obvious change in total composition or specific gravity (or weight), the law of equivoluminal metasomatism must be appropriate. It can be seen from the law of equivoluminal metasomatism that the above reaction equation is worthy to be discussed.

The left and right sides of the reaction equation balance the weights of reactant and resultant, but the law of equivoluminal metasomatism for solid minerals is not taken into consideration. We know that the weight of pure dolomite (or specific gravity) is roughly equivalent to that of pure talc (or specific gravity). While the weight of the former is $2.87g/cm^3$, the weight of the latter is $2.78g/cm^3$. Based on the thesis of Turner, the above reaction equation should abide by the law of equivoluminal metasomatism. Now the total gram-molecular volume of solid minerals on the left and right sides of the above reaction equation is calculated as follows [gram-molecular volume= (molecular weight/specific gravity)].

Reference Translation- may contain inconsistencies

$$3CaMg(CO_3) + 4SiO_2 + H_2O \longrightarrow Mg_3Si_4O_{10}(OH)_2$$

分子总体积　　198　　　　88　　　　　140

（厘米³）　　　　　286　　　　　　　　　　251

$$+ 3CaCO_3 + 2CO_2 \uparrow \quad \cdots\cdots\cdots\cdots\cdots(1)$$

——111
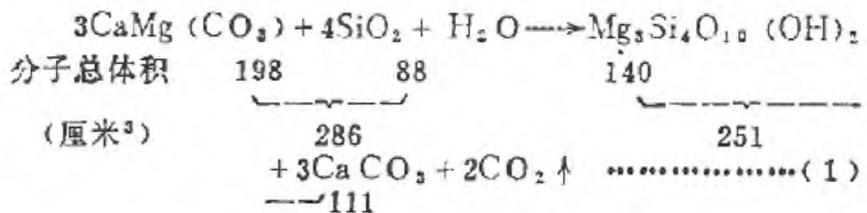
分子总体积	Total molecular volume
厘米 ³	cm³

Seen from the above reaction equation, the total molecular volume of solid minerals on the left and left sides of the reaction equation differs greatly. In this zone, the dolomite marble is directly replaced by talc and the content of calcite generated is small (less than 5%). In the above equation, the molecular volume of three gram molecules of dolomite is 198 cm³ and the molecular volume of one gram molecule of talc is 140cm³, so their molecular volume differs greatly and thus the law of equivoluminal metasomatism is not satisfied. According to the law of equivoluminal metasomatism, one gram molecule of talc only needs two gram molecules of dolomite (132 cm³). Therefore, the content of MgO in the dolomite is obviously insufficient. To meet the requirement for generating the talc, one gram molecule of MgO must be added from the external surrounding rocks, or else the pure dolomite marble cannot be metasomatized to generate the talc ore deposit that has the industrial value.
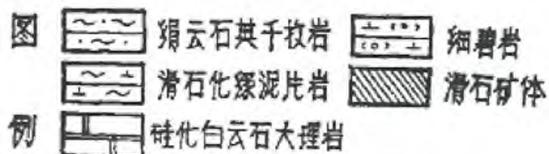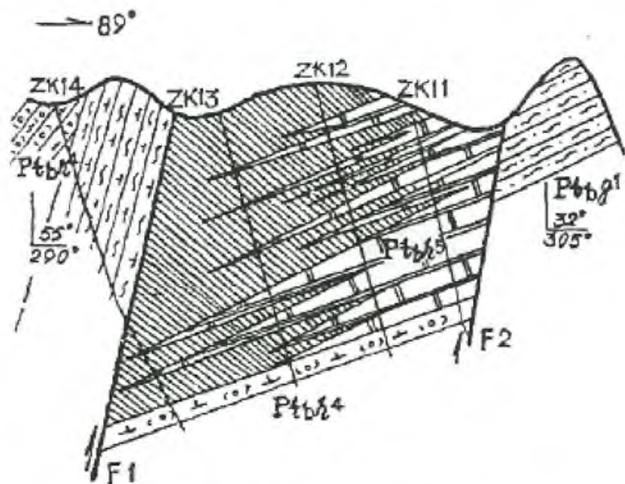
Figure 3 Geological profile of Line VII in the Lower Jizhua Mining District

Reference Translation- may contain inconsistencies

图例	Legend
绢云石英千枚岩	Sericite quartz phyllite
细碧岩	Spilite
滑石化绿泥石片岩	Talcous chlorite schist
滑石矿体	Talc ore body
硅化白云石大理岩	Silicified dolomite marble
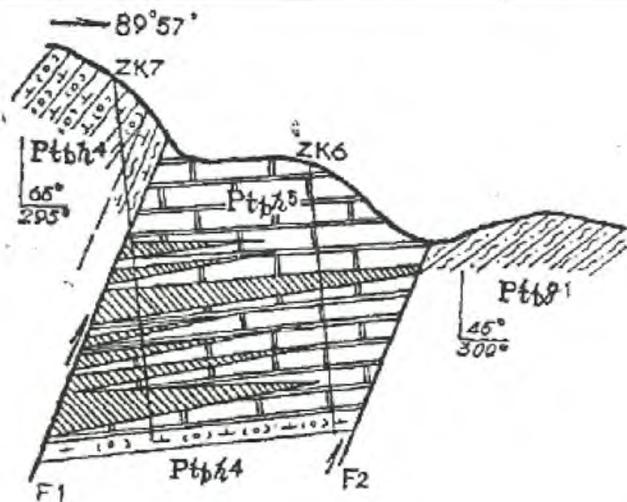
Figure 4 Geological profile of Line V in the Lower Jizhua Mining District

(the legend is the same as Figure 3)

In fact, although the single dolomite marble (ptbh^5) in this zone is cut by several regional NNE compressive fractures, the mineralization is not common as shown in Figure 3 and Figure 4. In the hanging wall of the compressive fracture F_2, the degree of mineralization of dolomite marble (ptbh^5) is quite weak because of the lack of MgO in the heading wall of formation (ptbh^1) containing sericite phyllite, slate and siliceous rock. In the mineralization process, MgO cannot be supplemented to the dolomite marble. On the contrary, the spilite containing a lot of MgO occurs in the hanging wall of the compressive fracture F_1 (containing 8.14% MgO on average). In the mineralization process, a lot of MgO can be supplemented to the dolomite marble, so the mineralization of dolomite marble that occurs near the compressive fracture F_1 is strong and the interlayers and remains of dolomite marble gradually decrease along the direction of spilite. To sum up, based on the geological features of mineralization of talc ores in this zone as well as the enrichment law, we think that it is suitable to take the following reaction equation (2):

$$2CaMg(CO_3)_2 + 4SiO_2 + MgO + H_2O \longrightarrow$$

分子总体积　　　132　　　88　　　11

（厘米³）　　　　　　　　231

$$Mg_3Si_4O_{10}(OH)_2 + 2CaCO_3 + 2CO_2 \uparrow \quad \cdots\cdots(2)$$

140　　　　　　　　　　　74

　　　　　214

分子总体积	Total molecular volume
厘米 ³	cm³

Where:

式中：　　　$2CaMg(CO_3)_2 + MgO \longrightarrow Mg_3Si_4O_{10}(OH)_2$

分子体积（厘米³）　　　132　　　11　　　　　　140

　　　　　　　143
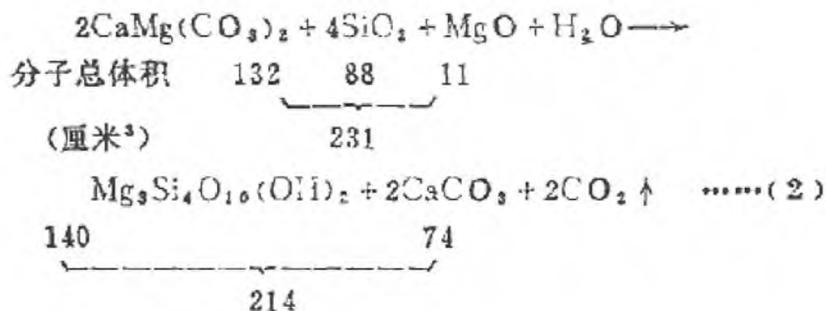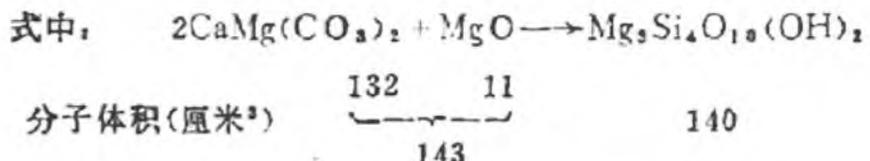
分子体积	Molecular volume
厘米 ³	cm³

In other words, the molecular volume of two gram molecules of dolomite and one gram molecule of MgO is 143 cm³, which is roughly equal to the molecular weight of one gram molecule of talc generated (140 cm³). Therefore, the law of equivoluminal metasomatism is basically satisfied and the genesis and enrichment law of talc ore deposit in this zone also can be objectively reflected.

2. Genesis Analysis of Talc Ore Deposit in This Zone

Seen from the above reaction equation (2), to learn about the genesis of talc ore deposit in this zone in detail, in addition to the investigation of geological conditions like ore-controlling fracture structure and mineralization mother rock-dolomite marble, it is also required to explore the cause and effect of conveying MgO to the metallogenic belt of surrounding rocks from the outside and also track the source of acid hydrothermal solution containing SiO_2. Now the geological features of mineralization in this zone are respectively discussed as follows:

Reference Translation- may contain inconsistencies

(1) Source of MgO

The mother rock that is directly related to mineralization is dolomite marble. This formation contains 19% MgO in this zone, so the requirement for generating the talc ore deposit cannot be completely satisfied and MgO must be absorbed from the external surrounding rock to supplement and the surrounding rock that satisfies this formation condition is spilite (ptbh[4]). In this zone, the content of MgO in spilite is 8.14% on average. Through rock-mineral determination and analysis, MgO is mainly concentrated in the tremolite (the content of tremolite in spilite is 30-35%). When the regional compressive fracture cuts the spilite, the spilite near the fracture zone is molten into the dynamic alteration zone of talcous chlorite schist under the action of strong extrusion and violent friction. This metamorphic zone varies from 10m to 40m in with, showing obvious schistosity, and the schistosity occurrence is roughly parallel to the fault plane. The talcous chlorite schist is mainly comprised of the chlorite. The main content in chlorite is the amesite that is altered from soda feldspar, clinozoisite and tremolite in the spilite. The secondary content in chlorite is the talc (the content is about 20%) that is altered from tremolite. In addition, the calcite assemblages or stringers as well as quartz stringers and gobbets are frequently seen. In the above alteration process, no matter whether the tremolite is altered into amesite or talc or part of the amesite is further altered into the talc under the action of compressive stress, a lot of MgO and SiO_2 as well as the hydrothermal solution of calcite (secondary hydrothermal solution) are decomposed so as to provide enough acid hydrothermal solution containing MgO and SiO_2 for generation into talc ores from dolomite marble. In the dynamic metamorphism process generated from fracture change, the alteration of minerals containing magnesium can be expressed by the following reaction equations:

① $Ca_2 Mg_6 Si_8 O_{22}(OH)_2 + 2CO_2 \longrightarrow$
透闪石

$Mg_3 Si_4 O_{10}(OH)_2 + 2CaCO_3 + MgO + 4SiO_2$
滑　石　　　　　　　　　　迁入白云石大理岩中

② $2Ca_2 Mg_5 Si_8 O_{22}(OH)_2 + 2CO_2 + H_2O \longrightarrow$
透闪石

$Mg_4 Si_4 O_{10}(OH)_8 + 2CaCO_3 + 4MgO + 12SiO_2$
镁绿泥石　　　　　　　　迁入白云石
　　　　　　　　　　　　大理岩中
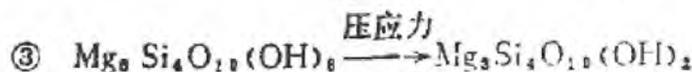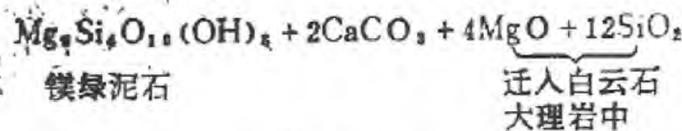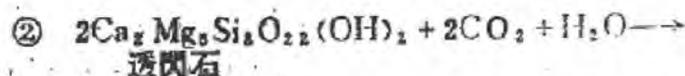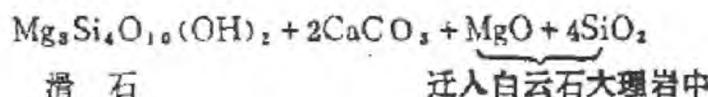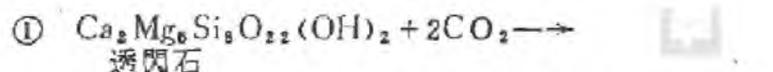
③ $Mg_6 Si_4 O_{10}(OH)_8 \xrightarrow{压应力} Mg_3 Si_4 O_{10}(OH)_2$
$+ 3MgO + 3H_2O$
迁入白云石大理岩中

b

透闪石	Tremolite

Reference Translation- may contain inconsistencies

滑石	Talc
迁入白云石大理岩中	Transferred into the dolomite marble
透闪石	Tremolite
镁绿泥石	Amesite
迁入白云石大理岩中	Transferred into the dolomite marble
压应力	Compressive stress
迁入白云石大理岩中	Transferred into the dolomite marble

The above reaction equations just can explain for the paragenetic association of minerals for talcous chlorite schist and also can reflect the genesis and enrichment factors of talc ores in this zone. Proven by the exploration work, the same ore deposit is located in the same ore-controlling fracture zone and the degree of mineralization of dolomite marble has an obvious superposition relationship with the width of alteration zone of the talcous chlorite schist in the hanging wall of fracture zone as shown in Figure 3 and Figure 4; if the alteration zone is wide, the degree of mineralization will be strong as shown in Figure 3; if the alteration zone becomes narrow, the degree of mineralization of dolomite marble will obviously decrease as shown in Figure 4. This is because the rich source of MgO is closely related to the alteration strength of spilite and thus the degree of mineralization of dolomite marble is directly affected.

(2) Hydrothermal Solution Containing SiO_2

The general acid hydrothermal solution containing SiO_2 comes from the magma. As above mentioned, the source of hydrothermal solution for mineralization (belonging to middle-low temperature) has no genesis relationship with the local magmatic rocks. It is thought through field observation that the source of acid hydrothermal solution containing SiO_2 used for generating the talc ore should be related to the dynamic metamorphism of regional compressive fracture. When searching along this type of fracture zone, it is found that the silicification degree and alteration nature of surrounding rocks near this fracture zone are closely related to the lithology of surrounding rocks in the hanging wall and the heading wall, especially the enrichment degree of SiO_2. By taking the fracture F_2 for an example, when this fracture cuts the formation (ptbg[1]) containing sericite quartz phyllite, slate and siliceous rock, the quartz dykes in the hanging wall and heading wall of this fracture zone are greatly developed, the rock silicification is very strong, secondary quartz rock and oil stone lodes are associated, and the dolomite marble is altered into the silicified marble. When this fracture cuts the single dolomite marble, the degree of silicification is relatively decreased and generally only the highly fractured zone is generated to form 16m-wide crushed marble as shown in Figure 5. When the compressive fracture cuts the spilite, besides the talcous chlorite schist, calcite and quartz stringers are also associated, but the silicification degree of rocks is still weak. Within the regional compressive ore-controlling fracture zone, the polymetallic mineralization

phenomenon is not yet found and the genesis of talc ores in this zone is hard to be explained by post-magmatic hydrothermal mineralization theory. It is thought by such scholars as Yeliseyev and Niggli that "the melting temperature of minerals will be reduced under the influence of directional pressure". Therefore, it can be thought that closed complex overturned fold and dense NNE imbricate compressive fracture are generated in the east wing of Sanmen complex overturned anticline in this zone due to the intensive concentration of NWW-SEE compressive stress. Due to the extremely strong change of this fracture and the substantial uplift of hanging wall, it is speculated that the vertical fault displacement is larger than 300m according to formation rupture and loss. Under such strong extrusion and violent friction, strong heat energy must be generated so as to melt the surrounding rocks near the fracture zone, especially the high-strength sericite quartz phyllite, slate and siliceous rock ($ptbg^1$-$ptbg^2$) etc. containing a large amount of SiO_2. After the surrounding rocks are molten, a large amount of secondary middle-low temperature acid hydrothermal solution containing SiO_2 as well as intermediate-acid dyke rocks (quartz diorite) can be generated so as to provide sufficient hydrothermal solution source for mineralization.
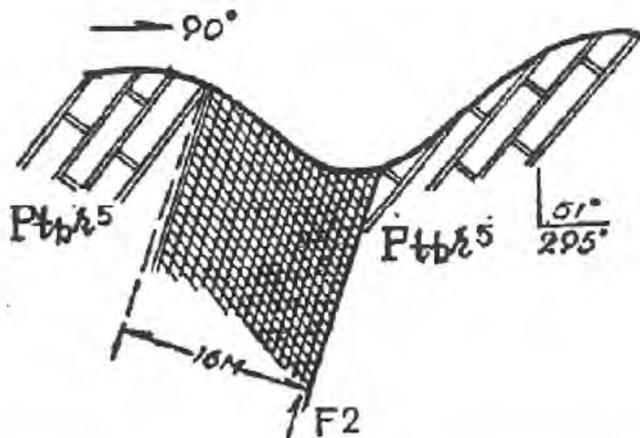
Figure 5 Fractured zone in the hanging wall of Fracture F_2 (the marble extruded into the cataclastic rock)

IV. Summary

1. The genesis of talc ore deposit in this zone should be the product of dynamic metamorphism. Therefore, the mineralization must be controlled by the regional NNE compressive fracture that is strongly active, and the hydrothermal solution source for mineralization is the derivative from the change of this fracture.

2. The dolomite marble is metasomatized into the talc ore by acid hydrothermal solution containing SiO_2. As their specific gravity (or weight) is roughly equal, the metasomatism must follow the equivoluminal principle. In other words, only two gram molecules of dolomite are required to generate one gram molecule of talc. Obviously, MgO in dolomite is insufficient and it must be supplemented from the external surrounding rock (spilite).

3. In this zone, the dolomite marble contacts with the spilite containing a large amount of MgO via

Reference Translation- may contain inconsistencies

the regional compressive fracture, which is a precondition for searching the talc ore. And the dynamic metamorphic zone of spilite as well as the development of talcous chlorite schist is an important factor for controlling the mineralization degree of dolomite marble.

Exhibit 33

Date	Exhibit #	Testing Entity	Author	Recipients	Purpose Stated	Test method	Mine	What was tested	Special Preperation	What tests revealed	Hopkins' Comments	Satisfies J&J Asbestos Defin
10/15/1957	J&J-309	Battelle	Smith					Italian talc		" the Italian talc averages about 10% fibrous or acicular particles"		
5/9/1958	J&J-1	Battelle	Smith	Dr. Lycan		petrograph	Val Chisone	processed talc italian 1		tremolite		
5/23/1958	J&J-2	Battelle	Smith	Dr. Lycan		microscope	Val Chisone	processed talc-Italian 1		tremolite; 6 to 10 % fibrous talc		
12/4/1970	J&J-9	Colorado School of Mines	Colorado School of Mines	Miller		XRD & petrograph	Hammondsville	38 core samples		tremolite-actinolite; fibrous talc		
3/9/1971	J&J-257	McCrone	Grieger	Goudie		SAED; XRD		Shower to Shower; medicated powder		"fiber of chrysotile.. Was very clear"; "medicated powder we found one fiber of chrysotile"; Shower to Shower...we feel stronglythat it may be chrysotile...chrysotile is very low"; >>> Final Report >>>"Shower to Shower The fiber content of Shower to Shower is quite low in comparison to previous samples which we have investigated...We found three suspect fibers . Of these, two were found in one field and probably have the same source, very possibly contamination...it is still questionable whether they are chrysotile. We have, however, found traces of chrysotile in G-11 one of the additives to Shower to Shower , and this might be a possible source of these contaminant fibers."		YES
5/14/1971	J&J-255	J&J	Ashton	Smith		XRD		Baby Powder (production batch)		tremolite; tremolite-actinolite		
7/2/1971	J&J-256	Colorado School of Mines	Pattengill	Ashton		XRD; PLM		six monthly plant run samples		5 of 6 show tremolite-actinolite; "no other forms of nontalc minerals approaching asbestos types were indentified"		
7/7/1971	J&J-15	Colorado School of Mines	Pattengill	Ashton		XRD	Vermont talc	processed talc-344-L		tremolite & actinolite		
7/29/1971	J&J-19	Colorado School of Mines, McCrone, Dartmouth	Nashed	Foster			Vermont talc			"trace amounts of fibrous minerals; (tremolite/actinolite) "		
10/12/1971	J&J-23	McCrone	Grieger	Goudie	appearance and fiber content	electron diffraction		Shower to Shower		traces of chrysotile in one of additives		YES
11/11/1971	J&J-376	McCrone	Grieger	Goudie		TEM		Shower to Shower		"The Shower to Shower appeared to have a few more fibers than the other two samples ,however I think that might be due to possible contamination from the G-11.In the G-11 we did find two positively identified chrysotile fibers and some other fibers which at first glance peeared to be chrysotile, when you look at the electron diffraction pattern. I believe that most of the fibers in Shower to Shower which are suspectmay come from G-11....I left out the comments on G-11from the report becuase I felt you might want to change your supplier or investigate your supplier , and this would only tend to confuse the issue perhapswith the FDA."		

Date	Doc#	Lab/Co	Name1	Name2	Purpose	Method	Location	Sample	Technique	Findings	Notes	Y/N
8/3/1972	J&J-28	NYU	Seymour Lewin	Dr. Weissler (FDA)		XRD		Shower to Shower sample 84		5% chrysotile;		YES
8/10/1972	J&J-373	J&J				PLM		Shower to Shower		"About 1 fiber or rod/needle every 500 particles. Approx. 1/3 of these are tremolite...."		
8/24/1972	J&J-29	Sperry Rand	Nashed	Dr. R. A. Fuller	FDA submits Lewin sample	SEM		Shower to Shower		"asbestos fibers could be detected in the sample"; "reported chrysotile"		YES
8/31/1972	J&J-348	Sperry Rand	JJ Wehrung			SEM		Shower to Shower		Dr. Weissler used SEM "to study general shape of chrysotile asbestos. " "Dr. Weissler he did find fibers which had the general shape of chrysotile". Also found "asbestos form fibers." In samples brought by JJ which were photographed."		
9/8/1972	D-7	Sperry Rand	JJ Wehrung			SEM		Shower to Shower		Observation of asbestosform "more correctly be called fiberform". SEM "very able to identify fiberforms which may be chrysotile"		
9/26/1972	J&J-31	Dr. Lewin	Dr. Nashed	Dr. Fuller				J&J Medicated Powder; Johnson's Baby Powder; J&J Shower to Shower		Medicated Powder: tremolite 4% Baby Powder: 2-3% chrysotile Shower to Shower: 2-5% chrysotile		YES
10/27/1972	J&J-36,34,37	McCrone	Stewart	Goudie	"the presence of asbestiform minerals"	XRD; TEM		Johnson's Baby Powder batch # 108T &109T (Lewin Samples)		"Both samples contained an insignificant amount of tremolite;" tremolite rods		YES
2/26/1973	J&J-100	Colorado School of Mines	Reid	Ashton	minerology & occurrence of any asbestos type minerals	XRD		processed talc	centrifuging	tremolite-actinolite; slight trace of anthophllite? Chrysotile? "asbestos type materials"		YES?
4/26/1973	J&J-44	J&J	Petterson	Johnston		PLM	Hammondsville	Johnson's Baby Powder		"tremolite or actinolite are indentifiable (optical microscope)and these might be classified as asbestos fiber"		No
4/27/1973	J&J-335	J&J				optical microscope		Johnson's Baby Powder		trace amounts of amphiboles in all samples. "The optical properties of the aprticles are closer to actinolite than tremolite"		
5/1/1973	J&J-367		Miller	Petterson			Haamondsville	ore		"the orde body contains tremolite"	Doesn't say which mine	
5/8/1973	J&J-368	J&J		Petterson			Hammondsville	ore		"Your question this morning was how did Lewin assay timing relate to actinolite showings. Baby Powder lots 108T & 109T were alleged to contain asbestiforms by Lewin. Talc shipments checked by microscope hare showed all lots clean just prior to and right after that time. the first showing of actinolite we know about is October 1972. The indications are that things were in good shape when Lewin picked up the above two lots for his assays."		
6/6/1973	J&J-47	Cardiff	Pooley	Ashton				our Vermont talc	concentration technique	actinolite		
9/6/1973	J&J-258	FDA	Stuart		"determination of asbestos	XRD; PLM		Shower to Shower sample 84		"fibers of tremolite/actinolite"		Yes
12/21/1973	J&J-263	Colorado School of Mines	Reid	Ashton	"examined for chrysotile and/or tremolite	TEM		Vermont talc samples	centrifuge	"identified chrysotile at a level of less than 10 ppm in the Vermont sample"		Yes

Date	ID	Lab	Name	Co.	Purpose	Method	Source	Sample	Procedure	Findings	Comments	Asbestos
1/29/1974	J&J-57	McCrone; Dartmouth		Lee		TEM; XRD	Hammondsville	ore & product		"chrysotile fiber suppression was indicated"; Dartmouth finds amphibole 100 to 200 ppm in ore and 3000 in ore; Mccrone finds chrysotile in ore and finished product		Yes
Mar-74	J&J-58	Dartmouth	Reynolds	Windsor Minerals	develop methods for measuring the concentration of asbestiform amphiboles"	XRD & XRF	talc product & ore from Windsor	ore & product	centrifuge to float talc and settle denser materials	"ore sample contains 2300ppm actinolite and the talc product contains 170 ppm actinolite"; "small amounts of anthophyllite may be present"	Dr. Hopkins has issues with the conclusions.	
4/24/1974	J&J-65	McCrone	Stewart	Zeitz	determine "whether or not there was any signficant content of asbestiform minerals "	XRD; TEM	Argonaut	ore		TEM finds chrysotile and fibrous tremolite		Yes
5/8/1974	J&J-66	McCrone				opticcal microscope & TEM		Windsor 66 ore & product		ore-fiber probably tremolite & chrysotile; product- one chrysotile fiber	Possible contamination of 1 test	YES
5/9/1974	J&J-366	McCrone				TEM	Argonaut	ore & product		chrysotile fibers in ore and product of 1/3 of samples tested		
5/14/1974	J&J-370	McCrone; Dartmouth	Zeitz			TEM	Hammondsville	Windsor 66 ore & product		Table 15 McCrone Summary-probable chrysotile in 2 samples and chrysotile in 2 other samples. >>>Attachment A Dated 05-08-74>>>>>>> "Sample 66-AC ore showed chrysotile fibers but in the product from the same ore benefaction had reduced the chrysotile content to 1 fibril as mentioned above. The chrysotile fiber content of Sample 66-AC-ore represents an estimated chrysotile content of<1-2 ppm, thus, even in the worst case, the level of asbestos contamination present in these ores is minimal.">>>>>>>>>>Attachment B>>>>>>>>>"fibrous form of anthophylite which occurs as a rare mineral in the Hammondsville ore body."		
10/10/1974	J&J-74	McCrone	Shimps	Zeitz	analysis for "asbestisform fibers"			product		"fibrous asbestisform material" "chrysotile fibers were found"		YES
7/1/1975	J&J-89	McCrone	Grieger	Zeitz	"determine the extent of amphibole or serpentine contamination" "we kept a running tabulation of the asbestos we could possibly identify"	TEM; SAED		"from your ore body"		"confirmed asbestos" low to medium; "bundles of amphiboles"		YES
9/9/1975	J&J-92	Mt. Sinai	Langer			TEM; PLM; XRD		Johnson's Baby Powder		anthophyllite & tremolite		
11/5/1975	J&J-97	McCrone	Grieger	Zeitz	supplement report of 7-01-75	TEM		ore		Table 1 lists "fibers of asbestos"		YES

Date	ID	Lab	Analyst 1	Analyst 2	Description	Method	Mine/Source	Sample	Findings	Notes	Yes
1/25/1977	J&J-141	Cardiff	Pooley			XRD		Vermont composite sample	fibers of antigorite		
6/14/1977	J&J -246	EMV				SEM; XRD		ore & product	composite samples-large and small fibrous tremolite	Source unknown-- Mr. Bicks says look in Metadata	YES?
2/9/1979	J&J-164	George Lee's Group	Cohen					66 composite samples	tremolite & actinolite		
9/1/1983	J&J-175	McCrone	Palenik	Miller	"airborne fiber concentrations"	NIOSH method	Argonaut; Rainbow	air samples	Argonaut - 118 fibers; Rainbow- 2650 fibers	Type of fiber not specified	YES
11/2/1984	J&J-179	McCrone	Palenik	Miller	"analysis for asbestos"	TEM- EPA method		air samples	6,600 to 60,000 chrysotile asbestos fibers. All samples found asbestos		YES
5/15/1985	J&J-177	MSHA	Olson		analysis for "asbestisform minerals"	PLM; XRD	Italian talc	air samples at Cyprus South Plainfield	71.2% fibrous talc & "5.8% anthophyllite, an asbestiform amphibole"		YES
8/5/1986	J&J-184	McCrone	Laubenthal	Miller		PCM	Hammondsville	air samples	fibers in both samples	Type of fiber not specified	YES
3/30/1987	J&J-185	J&J	Schmidt	Miller			Raymond Mill	Processed talc	"Tremolite is present in the fines (minus 100 plus 200 mesh) in six volume percent as free needles"		
4/15/1988	J&J-190	Skyline Laboratories; Aquatec Environmental				XRD	Chester/Hamm	random and composite process samples	actinolite		
2/25/1992	J&J-202	Cyprus	Munro				Argonaut; Hammonsdville; Black Bear	ore	"fibrous tremolite was identified..in exposures and cores at the east Argonaut 7 Black Bear mines. Cyprus staff report past tremolite from the Hammondsville and Clifton depositis."		
0/00/0000	J&J-298	McCrone						Windsor grade 36	chrysotile		
02/09/1979	J&J-341	J&J	Lee					Windsor 66 composite sample	"massive amphiboles in the 66 composite sample of Nov 6-10. the sample was forwarded to George Lee's group where the present of amphiboles was confirmed. They were identified as tremolite & actinolite"	duplicate of J&J 164	
05/09/1958	J&J-311	Battelle	Smith	J&J		Petrograph		Italian talc	"acicular and fibrous particles of talc"; the 8 to 10% of nonplaty talc is presumed to be derived from tremolite or enstatite"		
1/12/1984	J&J-305	McCrone	Palenik	Miller		PLM		Talc powder, grade EV	actinolite. The tremolite-actnolite in the sample is considered to be asbestos by current government regulations; however, it appeared to be cleavage fragments of the massive form rather than true asbestiform. typical tremolite fibers		
1/24/1958	J&J-310	Battelle	Brown	Lycan J&J				Italian talc	3 to 10% non platy with trace amounts of tremolite		
4/19/1973	J&J-296	J&J	Hamer			Dispersion staining		Johnson's Baby Powder	" four of the samples are suspected of containing tremolite based on the finding of one or two "fibers" per sample which satisfy the color/morphology criteria."		

Date	Number	Org			Purpose	Method		Sample	Finding	Notes
4/27/1973	J&J-335	J&J				Petrographic optical microscope		Johnson's Baby Powder	"trace amounts of amphibole" in all 4 samples tested; "Shape- prismatic, columnar, parallel – sided rods" ; Size: from 20X4 microns to 200X30 microns.; Indentity : the optical properties of the particles are closer to actinolite than tremolite"	
7/05/1976	J&J- 303	Colorado School of Mines				optical microscope		Johnson's Baby Powder	"small (1%?) amounts of amphibole needles."	
8/09/1972	J&J-342	J&J						Shower to Shower	"trace tremolite" in 1970 and 1971 samples	No chrysotile observed
8/27/1973	J&J-299	Dutch consumer organization				electron microscope (REM)		Johnson's Baby Powder	" asbestos – content of 1.59%"	
9/11/1975	J&J-297	McCrone	Stewart	Zeitz				A-HC	chrysotile fiber	Plate 4682 A-HC 51,000X Chrysotie fiber
9/18/1961	J&J-313	Battelle	Smith	Ashton		petrograph		Hammondsville core	2 percent non platy talc in upper core; 14% (granular and fibrous) non platy talc with 1-2% altered amphiboles in lower core	
??/??/????		Dutch Consumers						Johnson's Baby Powder	claimed to have found asbestos	
??/??/1972	J&J-33	University of Minnesota			determine possible content of fibrous chrysotile asbesots	TEM		Shower to Shower	"chrysotile asbestos does exist in the specimens of shower to shower"	
0/00/1991	J&J-327	Cypress	Munro				Argonaut mine		"Argonaut main ore body open pit ...high incidence of fibre bearing zones encountered in the main ore body"	
0/00/1991	J&J-327	Cypress	Munro				Hamm mine;		"areas with fibrous actinolite"	
7/9/??	J&J-17	Mt. Sinai	J&J			electron microscopy		Johnson's Baby Powder	chrysotile asbestos	
10/27/1972	J&J-26	J&J	Nashed	Goudie				Johnson's Baby Powder batch # 108T &109T (Lewin Samples)	"There are trace quantities [tremolite] present confrmed both by McCrone & BillAshton Levels are extremely lawbut occassionally can be seen optically. This is not new."	